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(54) Title: IMINOXYCARBOXYLATES AND DERIVATIVES AS INHIBITORS OF LEUKOTRIENE BIOSYNTHESIS

## (57) Abstract

The present invention relates to a compound of the formula: W-X-Q-Y-CH(R<sup>1</sup>)-O-N-C(R<sup>2</sup>)-A-COM, or a pharmaceutically acceptable salt thereof wherein W is optionally substituted aryl or heteroaryl; X is a valence bond, or methylene, divalent alkylene, alkenylene, alkynylene or alkyloxy; Q is a valence bond, or -O-, -S-, >NR<sup>4</sup> or >NCOR<sup>5</sup>; Y is optionally substituted phenyl, biphenyl, naphthyl, tetrahydronaphthyl, indolyl, pyridyl, or benzo[b]thienyl, thienyl, thiazolyl, or thiazolylphenyl; R<sup>1</sup> is alkyl, cycloalkyl, alkoxyalkyl, aryl or arylalkyl, heteroaryl or heteroarylalkyl; R<sup>2</sup> is hydrogen, alkyl or hydroxyalkyl; A is a valence bond or is selected from alkylene, alkenylene, alkynylene, cycloalkylene, phenylene, pyridylene, thienylene and furylene; and M is a pharmaceutically acceptable, metabolically cleavable group, -OR<sup>6</sup>, -NR<sup>6</sup>R<sup>7</sup>, -NH-tetrazoyl, -NH-2-, 3-, or 4-pyridyl, and -NH-2-, 4-, or 5-thiazolyl which inhibit leukotriene biosynthesis and are useful in the treatment of inflammatory disease states. Also disclosed are leukotriene biosynthesis inhibiting compositions and a method for inhibiting lipoxigenase activity and leukotriene biosynthesis.

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## IMINOXYCARBOXYLATES AND DERIVATIVES AS INHIBITORS OF LEUKOTRIENE BIOSYNTHESIS

### Technical Field

5        This invention relates to compounds having activity to inhibit lipxygenase enzymes, to pharmaceutical compositions comprising these compounds, and to a medical method of treatment. More particularly, this invention concerns oxime carboxylate compounds which inhibit leukotriene biosynthesis, to pharmaceutical compositions comprising these compounds and to a method of inhibiting leukotriene  
10        biosynthesis.

### Background of the Invention

      The leukotrienes are extremely potent substances which produce a wide variety of biological effects, often in the nanomolar to picomolar concentration range.  
15        Leukotrienes are important pathological mediators in a variety of diseases. Alterations in leukotriene metabolism have been demonstrated in a number of disease states including asthma, allergic rhinitis, rheumatoid arthritis and gout, psoriasis, adult respiratory distress syndrome, inflammatory bowel disease, endotoxin shock syndrome, atherosclerosis, ischemia induced myocardial injury, and central nervous  
20        system pathology resulting from the formation of leukotrienes following stroke or subarachnoid hemorrhage.

      Compounds which prevent leukotriene biosynthesis are thus useful in the treatment of disease states such as those listed above in which the leukotrienes play an important pathophysiological role.

25        United States Patent 4,970,215 to Mohrs *et al.* discloses and claims certain 4-(quinolin-2-yl-methoxy)phenyl-cycloalkylacetic acids for inhibiting leukotrienes synthesis.

      European Patent Application 0 349 062 to Zamboni *et al.* discloses and claims certain 2-quinolylmethoxyphenyl substituted thioalkanoic acid derivatives as  
30        leukotriene biosynthesis inhibitors. Prasit *et al.* in *Bioorganic and Medicinal Chemistry Letters* 1, 645-648 (1991) describe {[4-(4-chlorophenyl)-1-[4-(2-quinolylmethoxy)phenyl]butyl]thio}acetic acid, L-674,636, as a new, potent and orally active leukotriene synthesis inhibitor.

Summary of the Invention

In its principal embodiment, the present invention provides a compound of formula:



5 or a pharmaceutically acceptable salt thereof where n is zero or 1 with the proviso that n is zero when Y is tetrahydronaphthyl.

W is selected from (a) phenyl, (b) phenyl substituted with halogen, nitrile, alkyl of one to six carbon atoms, alkoxy of one to six carbon atoms, thiazolyl, thiazolyl substituted with halogen, alkyl of one to six carbon atoms, or alkoxy of one  
10 to six carbon atoms, pyridyl, or pyridyl substituted with halogen, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (c) naphthyl, (d) naphthyl substituted with halogen, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (e) pyridyl, (f) pyridyl substituted with (f-1) halogen, (f-2) alkyl of one to six carbon atoms, (f-3) alkoxy of one to six carbon atoms, (f-4) phenoxy, or  
15 (f-5) phenoxy substituted with halogen, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (g) quinolyl, (h) quinolyl substituted with halogen, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (i) benzothienyl, (j) benzothienyl substituted with halogen, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (k) benzothiazolyl, (l) benzothiazolyl substituted with  
20 halogen, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (l) benzoxazolyl, (m) benzoxazolyl substituted with halogen, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (n) benzimidazolyl, (o) benzimidazolyl substituted with halogen, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (p) quinoxaliny, (q) quinoxaliny substituted with halogen, alkyl of  
25 one to six carbon atoms, or alkoxy of one to six carbon atoms, (r) pyrimidyl, (s) pyrimidyl substituted with halogen, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (t) thiazolyl, (u) thiazolyl substituted with (u-1) halogen, (u-2) alkyl of one to six carbon atoms, (u-3) alkoxy of one to six carbon atoms, (u-4) phenyl, (u-5) phenyl substituted with halogen, alkyl of one to six carbon atoms, or  
30 alkoxy of one to six carbon atoms, (u-6) pyridyl, or (u-7) pyridyl substituted with halogen, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (v) pyridothiazolyl, and (w) pyridothiazolyl substituted with halogen, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms.

X is selected from alkylene of one to six carbon atoms, alkenylene of two to  
35 six carbon atoms, alkynylene of two to six carbon atoms, alkoxy of one to six carbon



atoms, thioalkyloxy of one to six carbon atoms, and alkylsulfonyl of one to six carbon atoms.

Q is a valence bond or is selected from -O-, -S-, >NR<sup>4</sup> where R<sup>4</sup> is hydrogen, or alkyl of one to six carbon atoms, and >NCOR<sup>5</sup> where R<sup>5</sup> is alkyl of one to six carbon atoms, amino, or alkylamino of one to six carbon atoms.

Y is selected from (a) phenyl, (b) phenyl substituted with halogen, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (c) biphenyl, (d) biphenyl substituted with halogen, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (e) naphthyl, (f) naphthyl substituted with halogen, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (g) tetrahydronaphthyl, (h) tetrahydronaphthyl substituted with halogen, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (i) indolyl, (j) indolyl substituted with halogen, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (k) benzothienyl, (l) benzothienyl substituted with halogen, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (m) pyridyl, (n) pyridyl substituted with halogen, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (o) thienyl, (p) thienyl substituted with halogen, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (q) thiazolyl, (r) thiazolyl substituted with halogen, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (s) benzo[b]furyl, (t) benzo[b]furyl substituted with halogen, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (u) benzo[b]thiazolyl, (v) benzo[b]thienyl substituted with halogen, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (w) thiazolylphenyl, and (x) thiazolylphenyl substituted with halogen, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms.

R<sup>1</sup> is selected from (a) alkyl of one to twelve carbon atoms, (b) cycloalkyl of three to ten carbon atoms, (c) cycloalkyl of three to ten carbon atoms containing one atom selected from -O-, -S-, >NR<sup>4</sup> where R<sup>4</sup> is hydrogen, or alkyl of one to six carbon atoms, and >NCOR<sup>5</sup> where R<sup>5</sup> is alkyl of one to six carbon atoms, amino, or alkylamino of one to six carbon atoms, (d) alkoxyalkyl in which the alkoxy and alkyl portions independently are of one to twelve carbon atoms, (e) phenyl, or phenyl substituted with halogen, alkyl of one to six carbon atoms, haloalkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (f) phenylalkyl in which the alkyl portion is of one to six carbon atoms, or phenylalkyl in which the phenyl ring is substituted with halogen, alkyl of one to six carbon atoms, haloalkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (g) pyridyl, or pyridyl substituted with halogen, alkyl of one to six carbon atoms, haloalkyl of one to six

carbon atoms, or alkoxy of one to six carbon atoms, (h) thiazolyl, or thiazolyl substituted with halogen, alkyl of one to six carbon atoms, haloalkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (i) thienyl, or thienyl substituted with halogen, alkyl of one to six carbon atoms, haloalkyl of one to six carbon atoms, 5 or alkoxy of one to six carbon atoms, (j) furyl, or furyl substituted with halogen, alkyl of one to six carbon atoms, haloalkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (k) oxazolyl, or oxazolyl substituted with halogen, alkyl of one to six carbon atoms, haloalkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (l) pyridazolyl, or pyridazolyl substituted with halogen, alkyl of one to 10 six carbon atoms, haloalkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (m) pyridylalkyl where the alkyl portion is of one to six carbon atoms, or pyridylalkyl in which the pyridyl ring is substituted with halogen, alkyl of one to six carbon atoms, haloalkyl of one to six carbon atoms, alkoxy of one to six carbon atoms, (n) thiazolylalkyl wherein the alkyl portion is of one to six carbon atoms, or 15 thiazolylalkyl in which the thiazolyl ring is substituted with halogen, alkyl of one to six carbon atoms, haloalkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (o) thienylalkyl where the alkyl portion is of one to six carbon atoms, or thienylalkyl in which the thienyl ring is substituted with halogen, alkyl of one to six carbon atoms, haloalkyl of one to six carbon atoms, or alkoxy of one to six 20 carbon atoms, (p) furylalkyl where the alkyl portion is of one to six carbon atoms, or furylalkyl in which the furyl ring is substituted with halogen, alkyl of one to six carbon atoms, haloalkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (q) oxazolylalkyl wherein the alkyl portion is of one to six carbon atoms, or oxazolylalkyl in which the oxazolyl ring is substituted with halogen, alkyl of one to 25 six carbon atoms, haloalkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, and (r) pyridazolylalkyl wherein the alkyl portion is of one to six carbon atoms, or pyridazolylalkyl in which the pyridazolyl ring is substituted with halogen, alkyl of one to six carbon atoms, haloalkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms.

30  $R^2$  is selected from hydrogen, alkyl of one to six carbon atoms, and hydroxyalkyl of one to six carbon atoms.

A is a valence bond or is selected from (a) alkylene of one to six carbon atoms, (b) cycloalkylene of three to eight carbon atoms, (c) phenyl, or phenyl substituted with halogen, alkyl of one to six carbon atoms, haloalkyl of one to six 35 carbon atoms, or alkoxy of one to six carbon atoms, (d) phenylalkyl in which the alkyl portion is of one to six carbon atoms, or phenylalkyl substituted with halogen,

alkyl of one to six carbon atoms, haloalkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (e) pyridyl, or pyridyl substituted with halogen, alkyl of one to six carbon atoms, haloalkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (f) thiazolyl, or thiazolyl substituted with halogen, alkyl of one to six carbon atoms, haloalkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (g) thienyl, or thienyl substituted with halogen, alkyl of one to six carbon atoms, haloalkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (h) furyl, or furyl substituted with halogen, alkyl of one to six carbon atoms, haloalkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (i) oxazolyl, or oxazolyl substituted with halogen, alkyl of one to six carbon atoms, haloalkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (j) pyridylalkyl wherein the alkyl portion is of one to six carbon atoms, or pyridylalkyl in which the pyridyl ring is substituted with halogen, alkyl of one to six carbon atoms, haloalkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (k) thiazolylalkyl wherein the alkyl portion is of one to six carbon atoms, or thiazolylalkyl in which the thiazolyl ring is substituted with halogen, alkyl of one to six carbon atoms, haloalkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (l) thienylalkyl where the alkyl portion is of one to six carbon atoms, or thienylalkyl in which the thienyl ring is substituted with halogen, alkyl of one to six carbon atoms, haloalkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (m) furylalkyl where the alkyl portion is of one to six carbon atoms, or furylalkyl in which the furyl ring is substituted with halogen, alkyl of one to six carbon atoms, haloalkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, (n) oxazolylalkyl wherein the alkyl portion is of one to six carbon atoms, or oxazolylalkyl where the oxazolyl ring is substituted with halogen, alkyl of one to six carbon atoms, haloalkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms.

**M** is selected from (a) a pharmaceutically acceptable, metabolically cleavable group, (b)  $-OR^6$  where  $R^6$  is selected from hydrogen or alkyl of one to six carbon atoms, (c)  $-NR^6R^7$  where  $R^7$  is selected from hydrogen, alkyl of one to six carbon atoms, hydroxy, alkoxy or one to six carbon atoms, or  $R^6$  and  $R^7$  taken together define a five- to eight-membered ring which may contain one or two additional oxygen, sulfur and nitrogen atoms, (d)  $-NH$ -tetrazoyl, (e)  $-NH$ -2-, 3-, or 4-pyridyl, and (f)  $-NH$ -2-, 4-, or 5-thiazolyl.

The present invention also provides pharmaceutical compositions which comprise a therapeutically effective amount of compound of Claim 1 in combination with a pharmaceutically acceptable carrier.

The invention further relates to a method of inhibiting leukotriene biosynthesis in a host mammal in need of such treatment comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.

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#### Detailed Description

As used throughout this specification and the appended claims, the following terms have the meanings specified.

The term alkyl refers to a monovalent group derived from a straight or branched chain saturated hydrocarbon by the removal of a single hydrogen atom.

10 Alkyl groups are exemplified by methyl, ethyl, *n*- and *iso*-propyl, *n*-, *sec*-, *iso*- and *tert*-butyl, and the like.

The terms alkoxy and alkoxyl denote an alkyl group, as defined above, attached to the parent molecular moiety through an oxygen atom. Representative alkoxy groups include methoxy, ethoxy, propoxy, butoxy, and the like.

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The terms alkenyl as used herein refer to monovalent straight or branched chain groups of 2 to 6 carbon atoms containing a carbon-carbon double bond, derived from an alkene by the removal of one hydrogen atom and include, but are not limited to groups such as ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like.

20

The term alkylene denotes a divalent group derived from a straight or branched chain saturated hydrocarbon containing by the removal of two hydrogen atoms, for example -CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>-, -CH(CH<sub>3</sub>)CH<sub>2</sub>- and the like.

The term alkenylene denotes a divalent group derived from a straight or branched chain hydrocarbon containing at least one carbon-carbon double bond.

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Examples of alkenylene include -CH=CH-, -CH<sub>2</sub>CH=CH-, -C(CH<sub>3</sub>)=CH-, -CH<sub>2</sub>CH=CHCH<sub>2</sub>-, and the like.

The terms alkynylene refers to a divalent group derived by the removal of two hydrogen atoms from a straight or branched chain acyclic hydrocarbon group containing at least one carbon-carbon triple bond. Examples of alkynylene include

30

-CH≡CH-, -CH≡C-CH<sub>2</sub>-, -CH≡CH-CH(CH<sub>3</sub>)- and the like.

The term aryl as used herein refers to a monovalent carbocyclic group containing one or more fused or non-fused phenyl rings and includes, for example, phenyl, 1- or 2-naphthyl, 1,2-dihydronaphthyl, 1,2,3,4-tetrahydronaphthyl, and the like.

The term cycloalkyl as used herein refer to a monovalent saturated cyclic hydrocarbon group. Representative cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[2.2.1]heptane and the like.

Cycloalkylene denotes a divalent radical derived from a cycloalkane by the removal of two hydrogen atoms.

The term haloalkyl denotes an alkyl group, as defined above, having one, two, or three halogen atoms attached thereto and is exemplified by such groups as chloromethyl, bromoethyl, trifluoromethyl, and the like.

The term metabolically cleavable group denotes a group which is cleaved *in vivo* to yield the parent molecule of the formula I indicated above wherein M is hydrogen. Examples of metabolically cleavable groups include -COR, -COOR, -CONRR and -CH<sub>2</sub>OR radicals where R is selected independently at each occurrence from alkyl, trialkylsilyl, carbocyclic aryl or carbocyclic aryl substituted with one or more of C<sub>1</sub>-C<sub>4</sub> alkyl, halogen, hydroxy or C<sub>1</sub>-C<sub>4</sub> alkoxy. Specific examples of representative metabolically cleavable groups include acetyl, methoxycarbonyl, benzoyl, methoxymethyl and trimethylsilyl groups.

The terms phenylene, pyridylene, thienylene, and furylene refer to divalent radicals derived by the removal of two hydrogen atoms from the ring systems of benzene, pyridine, thiophene, and furan, respectively.

By pharmaceutically acceptable salt it is meant those salts which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M Berge, *et al.* describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, 66:1 - 19. The salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or separately by reacting the free base function with a suitable organic acid. Representative acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphersulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate,

thiocyanate, toluenesulfonate, undecanoate, valerate salts, and the like.

Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, 5 tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like.

Asymmetric centers may exist in the compounds of the present invention. The present invention contemplates the various stereoisomers and mixtures thereof. Individual stereoisomers of compounds of the present invention are made by 10 synthesis from starting materials containing the chiral centers or by preparation of mixtures of enantiomeric products followed by separation as, for example, by conversion to a mixture of diastereomers followed by separation by recrystallization or chromatographic techniques, or by direct separation of the optical enantiomers on chiral chromatographic columns. Starting compounds of particular stereochemistry 15 are either commercially available or are made by the methods detailed below and resolved by techniques well known in the organic chemical arts.

Compounds contemplated as falling within the scope of the present invention include, but are not limited to

[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]iminoxyacetic acid,

20 [cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxy propionic acid,

[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-4-iminoxy pentanoic acid,

[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxy-3-(4-hydroxyphenyl)propionic acid,

[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxy-3-phenylpropionic 25 acid,

O-[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-4-carboxybenzaloxime,

[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-3-iminoxy-(2,2-dimethyl)propionic acid,

[cyclopentyl-(4-(2-quinolylmethoxy)phenyl)methyl]iminoxy acetic acid,

30 [cyclopentyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxy propionic acid,

[1,2,3,4-tetrahydro-6-(2-quinolylmethoxy)naphth-1-yl]iminoxy acetic acid,

[1,2,3,4-tetrahydro-6-(2-quinolylmethoxy)naphth-1-yl]-2-iminoxypropionic acid,

[4-(4-chlorophenyl)-1-(4-(2-quinolylmethoxy)phenyl)butyl]iminoxyacetic acid,

[2-cyclohexyl-1-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]iminoxyacetic acid,

35 O-[2-cyclohexyl-1-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]-4-carboxybenzaloxime,

[2-cyclohexyl-1-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]-2-iminoxypropionic acid,

- [2-cyclohexyl-1-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]-4-iminoxypentanoic acid,  
[cycloheptyl-(4-(2-quinolylmethoxy)phenyl)methyl]iminoxy acetic acid,  
[3-cyclohexyl-2-(4-(2-quinolylmethoxy)phenyl)prop-1-yl]iminoxy acetic acid,  
[3-cyclohexyl-2-(4-(2-quinolylmethoxy)phenyl)prop-1-yl]-2-iminoxypropionic acid,  
5 [3-cyclohexyl-2-(4-(2-quinolylmethoxy)phenyl)prop-1-yl]-3-iminoxy-(2,2-  
dimethyl)propionic acid,  
[4-(4-fluorophenyl)-1-(4-(2-quinolylmethoxy)phenyl)but-1-yl] iminoxyacetic acid,  
[4-(4-fluorophenyl)-1-(4-(2-quinolylmethoxy)phenyl)but-1-yl]-2-iminoxypropionic  
acid,  
10 [2-cyclohexyl-2-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]iminoxyacetic acid,  
[2-cycloheptyl-2-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]iminoxyacetic acid,  
[2-cycloheptyl-2-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]-3-iminoxy-2,2-  
dimethylpropionic acid,  
[2-cyclopentyl-2-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]iminoxyacetic acid,  
15 [cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-Z-2-iminoxypropionic acid  
methyl ester,  
[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-E-2-iminoxypropionic acid  
methyl ester,  
[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-Z-2-iminoxy propionic acid,  
20 [cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-E-2-iminoxy propionic acid,  
(R)-[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-E-2-iminoxypropionic acid  
methyl ester,  
(R)-[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-E-2-iminoxypropionic acid,  
(S)-[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-E-2-iminoxypropionic acid  
25 methyl ester,  
(S)-[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-E-2-iminoxypropionic acid,  
[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-Z-iminoxy acetic acid methyl  
ester,  
[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-E-iminoxy acetic acid methyl  
30 ester,  
[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-E-iminoxy acetic acid,  
[2-phenyl-1-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]-Z-2-iminoxy propionic acid,  
[2-phenyl-1-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]-E-2-iminoxy propionic acid,  
[2-thienyl-(4-(2-quinolylmethoxy)phenyl)methyl]-E-2-iminoxy propionic acid,  
35 [cyclohexyl-(2-chloro-4-(2-quinolylmethoxy)phenyl)methyl]-E-2-iminoxypropionic  
acid,

- [cyclohexyl-(3-chloro-4-(2-quinolylmethoxy)phenyl)methyl]-*E*-2-iminoxypropionic acid,  
[cyclohexyl-(2-chloro-4-(2-quinolylmethoxy)phenyl)methyl]-*Z*-2-iminoxypropionic acid,  
5 [3-methyl-3-phenyl-1-[4-(2-quinolylmethoxy)phenyl]but-1-yl]-*Z*-2-iminoxypropionic acid,  
[3-methyl-3-phenyl-1-(4-(2-quinolylmethoxy)phenyl)but-1-yl]-*E*-2-iminoxypropionic acid,  
[3-methyl-3-phenyl-1-(4-(2-quinolylmethoxy)phenyl)but-1-yl]-*E*-2-iminoxyacetic  
10 acid,  
[4-(2-quinolylmethoxy)phenyl]pent-1-yl]-*E*-2-iminoxypropionic acid,  
[4-(2-quinolylmethoxy)phenyl]pent-1-yl]-*E*-iminoxyacetic acid,  
[4-(2-quinolylmethoxy)phenyl]-but-3-en-1-yl]-*E*-iminox-2-propionic acid,  
[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*E*-2-iminox butanoic acid,  
15 [cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*E*-3-iminoxbutanoic acid,  
[cyclohexyl-1-(4-(2-quinolylmethoxy)phenyl)eth-2-yl]-2-iminox propionic acid,  
[cycloheptyl-(4-(2-quinolylmethoxy)phenyl)eth-2-yl]-2-iminox propionic acid,  
[2-chloro-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminox propionic acid,  
[cycloheptyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminox propionic acid,  
20 Sodium [cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypropionate,  
(*R*)-[cyclopentyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*E*-2-iminoxypropionic acid,  
(*S*)-[cyclopentyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*E*-2-iminoxypropionic acid,  
[cyclohexyl-(4-(2-quinolylmethoxy)benzo[*b*]thien-2-yl)methyl]-2-iminoxypropionic  
acid,  
25 [cyclohexyl-(6-(2-quinolylmethoxy)pyrid-3-yl)methyl]iminox acetic acid,  
[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminox propionic acid 2-  
thiazolamide,  
[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminox propionic acid 2-  
pyridylamide,  
30 [cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypropionic acid 5-  
tetrazylamide,  
[cyclohexyl-(4-(6-(4-fluorophenoxy)pyrid-2-ylmethoxy)phenyl)methyl]iminox  
acetic acid,  
[2-cyclohexyl-1-(4-(4-thiazolylmethoxy)phenyl)eth-1-yl]iminox acetic acid,  
35 *O*-[2-cyclohexyl-1-(4-(4-thiazolylmethoxy)phenyl)eth-1-yl]-4-carboxybenzaloxime,  
[2-cyclohexyl-1-(4-(4-thiazolylmethoxy)phenyl)eth-1-yl]-2-iminoxypropionic acid,



- [cyclohexyl-(4-(4-thiazolylmethoxy)phenyl)methyl]-2-iminoxy propionic acid,  
[cyclohexyl-(4-(4-thiazolylmethoxy)phenyl)methyl]iminoxyacetic acid,  
[cyclohexyl-(4-(2-benzothiazolylmethoxy)phenyl)methyl]iminoxy acetic acid,  
[cyclohexyl-(4-(1-methyl-2-benzimidazolylmethoxy)phenyl) methyl]-2-  
5 iminoxypropionic acid,  
[cyclohexyl-(4-(2-benzoxazolylmethoxy)phenyl)methyl]iminoxy acetic acid,  
[cyclohexyl-(4-(4-pyridylmethoxy)phenyl)methyl]-2-iminoxypropionic acid,  
[cyclohexyl-(4-(3-pyridylmethoxy)phenyl)methyl]-2-iminoxypropionic acid,  
[cyclohexyl-(4-(2-pyridylmethoxy)phenyl)methyl]-2-iminoxypropionic acid,  
10 [cyclohexyl-(4-(2-thiazolylmethoxy)phenyl)methyl]-2-iminoxypropionic acid,  
[cyclohexyl-(4-(4-thiazolylmethoxy)phenyl)methyl]-2-iminoxypropionic acid,  
[cyclohexyl-(4-(5-thiazolylmethoxy)phenyl)methyl]-2-iminoxypropionic acid,  
[cyclohexyl-(4-(2-quinolylmethoxy)phenyl-4-phenyl)methyl]-2-iminoxypropionic  
acid,  
15 [cyclohexyl-(6-(2-quinolylmethoxy)naphth-2-yl)methyl]-2-iminoxypropionic acid,  
[cyclohexyl-(6-(2-quinolylmethoxy)-1,2,3,4-tetrahydronaphth-2-yl)methyl]-2-  
iminoxypropionic acid,  
[cyclohexyl-(1-methyl-6-(2-quinolylmethoxy)indol-2-yl)methyl]-2-iminoxypropionic  
acid,  
20 [cycloheptyl-(6-(2-quinolylmethoxy)benzo[b]thien-2-yl)methyl]-2-iminoxypropionic  
acid,  
[cyclohexyl-(4-(2-quinolylethyl)phenyl)methyl]-2-iminoxypropionic acid,  
[cyclohexyl-(4-(2-quinolylethenyl)phenyl)methyl]-2-iminoxypropionic acid,  
[cyclohexyl-(4-(2-quinolyloxymethyl)phenyl)methyl]-2-iminoxypropionic acid,  
25 [cyclohexyl-(4-(2-quinolylthiomethyl)phenyl)methyl]-2-iminoxypropionic acid,  
[cyclohexyl-(4-(2-quinolylsulfonylmethyl)phenyl)methyl]-2-iminoxypropionic acid,  
[cyclohexyl-(4-(2-quinolylethynyl)phenyl)methyl]-2-iminoxypropionic acid,  
[cyclohexyl-(4-(2-quinolylmethoxyethyl)phenyl)methyl]-2-iminoxypropionic acid,  
[cyclohexyl-(2-(2-pyridylmethoxy)pyrid-5-yl)methyl]-2-iminoxypropionic acid,  
30 [cyclohexyl-(5-(2-quinolylmethoxy)thien-2-yl)methyl]-2-iminoxypropionic acid,  
[cyclohexyl-(2-(2-quinolylmethoxy)thien-5-yl)methyl]-2-iminoxypropionic acid,  
[cyclohexyl-(6-(2-quinolylmethoxy)benzo[b]fur-2-yl)methyl]-2-iminoxypropionic  
acid,  
[cyclopentyl-(4-(2-quinoxalylmethoxy)phenyl)methyl]-2-iminoxypropionic acid,  
35 [cyclohexyl-(4-(thiazolo[4,5-b]pyrid-6-ylmethoxy)phenyl)methyl]-2-  
iminoxypropionic acid,

- [cyclohexyl-(4-(thiazolo[5,4-b]pyrid-6-ylmethoxy)phenyl)methyl]-2-iminoxypionic acid,
- [cyclopentyl-(4-(2-pyrimidylmethoxy)phenyl)methyl]-2-iminoxypionic acid,
- [cyclohexyl-(4-(4-phenylthiazol-2-ylmethoxy)phenyl)methyl]-2-iminoxypionic acid,
- 5 [cyclohexyl-(4-((4-pyrid-2-yl)thiazol-2-ylmethoxy)phenyl)methyl]-2-iminoxypionic acid,
- [phenyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypionic acid,
- [5-methylthien-2-yl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypionic acid,
- 10 [pyrid-2-yl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypionic acid,
- [3-cyclopropylpropyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypionic acid,
- [butyloxymethyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypionic acid,
- [2-phenylethyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypionic acid,
- 15 [2-pyrid-4-ylethyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypionic acid,
- [2-furyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypionic acid,
- [2-thiazolyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypionic acid,
- [4-perhydropyranyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypionic acid,
- (R)-[cyclohexyl-(4-(2-benzothiazolylmethoxy)phenyl)methyl]iminoxy acetic acid,
- 20 (S)-[cyclohexyl-(4-(2-benzothiazolylmethoxy)phenyl)methyl]iminoxy acetic acid,
- [cyclopentyl-(4-(2-benzothiazolylmethoxy)phenyl)methyl]iminoxy acetic acid.
- (R)-[cyclopentyl-(4-(2-benzothiazolylmethoxy)phenyl)methyl]iminoxy acetic acid,
- (S)-[cyclopentyl-(4-(2-benzothiazolylmethoxy)phenyl)methyl]iminoxy acetic acid,
- 25 [2-cyclopentyl-1-(4-(4-thiazolylmethoxy)phenyl)eth-1-yl]iminoxy acetic acid,
- O*-[2-cyclopentyl-1-(4-(4-thiazolylmethoxy)phenyl)eth-1-yl]-4-carboxybenzaldoxime,
- [2-cyclopentyl-1-(4-(4-thiazolylmethoxy)phenyl)eth-1-yl]-2-iminoxypionic acid,
- [cyclopentyl-(4-(4-thiazolylmethoxy)phenyl)methyl]-2-iminoxy propionic acid,
- [cyclopentyl-(4-(4-thiazolylmethoxy)phenyl)methyl]iminoxyacetic acid,
- 30 (R)-[cyclohexyl-(4-(6-(4-fluorophenoxy)pyrid-2-ylmethoxy)phenyl)methyl]iminoxyacetic acid,
- (S)-[cyclohexyl-(4-(6-(4-fluorophenoxy)pyrid-2-ylmethoxy)phenyl)methyl]iminoxyacetic acid,
- [cyclopentyl-(4-(6-(4-fluorophenoxy)pyrid-2-ylmethoxy)phenyl)methyl]iminoxyacetic acid,
- 35 [cyclopentyl-(4-(6-(4-fluorophenoxy)pyrid-2-ylmethoxy)phenyl)methyl]iminoxyacetic acid,

- (R)-[cyclopentyl-(4-(6-(4-fluorophenoxy)pyrid-2-ylmethoxy)phenyl)methyl]iminoxyacetic acid,  
(S)-[cyclopentyl-(4-(6-(4-fluorophenoxy)pyrid-2-ylmethoxy)phenyl)methyl]iminoxyacetic acid.
- 5 [cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]iminoxyaceto-*N*-hydroxyamide,  
[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxy propionyl-*N*-methyl-*N*-hydroxyamide,  
[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-4-iminoxy pentanoyl-*N*-methyl-*N*-hydroxyamide,
- 10 [cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxy-3-(4-hydroxyphenyl)propionyl-*N*-methyl-*N*-hydroxyamide,  
[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxy-3-phenylpropionyl-*N*-methyl-*N*-hydroxyamide,  
[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-3-iminoxy-(2,2-dimethyl)
- 15 propionyl-*N*-methyl-*N*-hydroxyamide,  
[cyclopentyl-(4-(2-quinolylmethoxy)phenyl)methyl]iminoxyaceto-*N*-hydroxyamide,  
[cyclopentyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxy propionyl-*N*-methyl-*N*-hydroxyamide,
- 20 [1,2,3,4-tetrahydro-6-(2-quinolylmethoxy)naphth-1-yl]iminoxy aceto-*N*-hydroxyamide,  
[1,2,3,4-tetrahydro-6-(2-quinolylmethoxy)naphth-1-yl]-2-iminoxypropionyl-*N*-methyl-*N*-hydroxyamide,  
[4-(4-chlorophenyl)-1-(4-(2-quinolylmethoxy)phenyl)butyl]iminoxyaceto-*N*-hydroxyamide,
- 25 [2-cyclohexyl-1-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]iminoxyaceto-*N*-hydroxyamide,  
[2-cyclohexyl-1-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]-2-iminoxypropionyl-*N*-methyl-*N*-hydroxyamide,  
[2-cyclohexyl-1-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]-4-iminoxypentanoyl-*N*-methyl-*N*-hydroxyamide,
- 30 [cycloheptyl-(4-(2-quinolylmethoxy)phenyl)methyl]iminoxyaceto-*N*-hydroxyamide,  
[3-cyclohexyl-2-[4-(2-quinolylmethoxy)phenyl]prop-1-yl]iminoxy aceto-*N*-hydroxyamide,  
[3-cyclohexyl-2-(4-(2-quinolylmethoxy)phenyl)prop-1-yl]-2-iminoxypropionyl-*N*-methyl-*N*-hydroxyamide,
- 35

- [3-cyclohexyl-2-(4-(2-quinolylmethoxy)phenyl)prop-1-yl]-3-iminoxy-(2,2-dimethyl)propionyl-*N*-methyl-*N*-hydroxyamide,  
[4-(4-fluorophenyl)-1-(4-(2-quinolylmethoxy)phenyl)but-1-yl] iminoxyaceto-*N*-hydroxyamide,  
5 [4-(4-fluorophenyl)-1-(4-(2-quinolylmethoxy)phenyl)but-1-yl]-2-iminoxypropionyl-*N*-methyl-*N*-hydroxyamide,  
[2-cyclohexyl-2-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]iminoxyaceto-*N*-hydroxyamide,  
[2-cycloheptyl-2-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]iminoxyaceto-*N*-hydroxyamide,  
10 [2-cycloheptyl-2-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]-3-iminoxy-2,2-dimethylpropionyl-*N*-methyl-*N*-hydroxyamide,  
[2-cyclopentyl-2-(4-(2-quinolylmethoxy)phenyl)eth-1-yl] iminoxyaceto-*N*-hydroxyamide,  
15 [cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*Z*-2-iminoxypropionyl-*N*-methyl-*N*-hydroxyamide,  
[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*E*-2-iminoxypropionyl-*N*-methyl-*N*-hydroxyamide,  
(*R*)-[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*E*-2-iminoxypropionyl-*N*-methyl-*N*-hydroxyamide,  
20 (*S*)-[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*E*-2-iminoxypropionyl-*N*-methyl-*N*-hydroxyamide,  
[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*E*-iminoxy aceto-*N*-hydroxyamide,  
25 [2-phenyl-1-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]-*Z*-2-iminoxypropionyl-*N*-methyl-*N*-hydroxyamide,  
[2-phenyl-1-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]-*E*-2-iminoxy propionyl-*N*-methyl-*N*-hydroxyamide,  
[2-thienyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*E*-2-iminoxy propionyl-*N*-methyl-*N*-hydroxyamide,  
30 [cyclohexyl-(2-chloro-4-(2-quinolylmethoxy)phenyl)methyl]-*E*-2-iminoxypropionyl-*N*-methyl-*N*-hydroxyamide,  
[cyclohexyl-(3-chloro-4-(2-quinolylmethoxy)phenyl)methyl]-*E*-2-iminoxypropionyl-*N*-methyl-*N*-hydroxyamide,  
35 [cyclohexyl-(2-chloro-4-(2-quinolylmethoxy)phenyl)methyl]-*Z*-2-iminoxypropionyl-*N*-methyl-*N*-hydroxyamide,

- [3-methyl-3-phenyl-1-[4-(2-quinolylmethoxy)phenyl]but-1-yl]-Z-2-  
iminoxypropionyl-*N*-methyl-*N*-hydroxyamide,  
[3-methyl-3-phenyl-1-(4-(2-quinolylmethoxy)phenyl)but-1-yl]-*E*-2-  
iminoxypropionyl-*N*-methyl-*N*-hydroxyamide,  
5 [cyclohexyl-(2-chloro-4-(2-quinolylmethoxy)phenyl)methyl]-Z-2-iminoxypropionyl-  
*N*-methyl-*N*-hydroxyamide,  
[3-methyl-3-phenyl-1-[4-(2-quinolylmethoxy)phenyl]but-1-yl]-Z-2-  
iminoxypropionyl-*N*-methyl-*N*-hydroxyamide,  
[3-methyl-3-phenyl-1-(4-(2-quinolylmethoxy)phenyl)but-1-yl]-*E*-2-  
10 iminoxypropionyl-*N*-methyl-*N*-hydroxyamide,  
[4-(2-quinolylmethoxy)phenylpent-1-yl]-*E*-2-iminoxypropionyl-*N*-methyl-*N*-  
hydroxyamide,  
[4-(2-quinolylmethoxy)phenyl]pent-1-yl]-*E*-iminoxyaceto-*N*-hydroxyamide,  
[4-(2-quinolylmethoxy)phenyl]-but-3-en-1-yl]-*E*-iminoxy-2-propionyl-*N*-methyl-*N*-  
15 hydroxyamide,  
[cyclohexyl-1-(4-(2-quinolylmethoxy)phenyl)eth-2-yl]-2-iminoxypropionyl-*N*-  
methyl-*N*-hydroxyamide,  
[cycloheptyl-(4-(2-quinolylmethoxy)phenyl)eth-2-yl]-2-iminoxypropionyl-*N*-methyl-  
*N*-hydroxyamide,  
20 [2-chloro-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypropionyl-*N*-methyl-*N*-  
hydroxyamide,  
[cycloheptyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypropionyl-*N*-methyl-  
*N*-hydroxyamide,  
(*R*)-[cyclopentyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*E*-2-iminoxypropionyl-*N*-  
25 methyl-*N*-hydroxyamide,  
(*S*)-[cyclopentyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*E*-2-iminoxypropionyl-*N*-  
methyl-*N*-hydroxyamide,  
[cyclohexyl-(4-(2-quinolylmethoxy)benzo[*b*]thien-2-yl)methyl]-2-iminoxypropionyl-  
*N*-methyl-*N*-hydroxyamide,  
30 [cyclohexyl-(6-(2-quinolylmethoxy)pyrid-3-yl)methyl]iminoxy aceto-*N*-  
hydroxyamide,  
[cyclohexyl-(4-(6-(4-fluorophenoxy)pyrid-2-  
ylmethoxy)phenyl)methyl]iminoxyaceto-*N*-hydroxyamide  
[2-cyclohexyl-1-(4-(4-thiazolylmethoxy)phenyl)eth-1-yl]iminoxyaceto-*N*-  
35 hydroxyamide,

[2-cyclohexyl-1-(4-(4-thiazolylmethoxy)phenyl)eth-1-yl]-2-iminoxypropionyl-*N*-methyl-*N*-hydroxyamide,  
[cyclohexyl-(4-(4-thiazolylmethoxy)phenyl)methyl]-2-iminoxy propionyl-*N*-methyl-*N*-hydroxyamide,  
5 [cyclohexyl-(4-(4-thiazolylmethoxy)phenyl)methyl]iminoxyaceto-*N*-hydroxyamide,  
[cyclohexyl-(4-(2-benzothiazolylmethoxy)phenyl)methyl]iminoxyaceto-*N*-hydroxyamide,  
[cyclohexyl-(4-(1-methyl-2-benzimidazolylmethoxy)phenyl)methyl]-2-iminoxypropionyl-*N*-methyl-*N*-hydroxyamide, and  
10 [cyclohexyl-(4-(2-benzoxazolylmethoxy)phenyl)methyl]iminoxyaceto-*N*-hydroxyamide.

In one preferred embodiment, compounds of this invention have the formula shown above wherein **W** is pyridyl, or pyridyl substituted with halogen, alkyl of one  
15 to six carbon atoms, alkoxy of one to six carbon atoms, phenoxy, or phenoxy substituted with halogen, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, **X** is methylene, **Q** is -O-, and **Y** is phenyl.

In another preferred embodiment, compounds of this invention have the formula shown above wherein **W** is thiazolyl, or thiazolyl substituted with halogen,  
20 alkyl of one to six carbon atoms, alkoxy of one to six carbon atoms, phenyl, phenyl substituted with halogen, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, pyridyl, or pyridyl substituted with halogen, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms.

In yet another preferred embodiment, compounds of this invention have the formula shown above wherein **W** is benzothiazolyl, or benzothiazolyl substituted  
25 with halogen, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, **X** is methylene, **Q** is -O-, and **Y** is phenyl.

In a more preferred embodiment, compounds of the present invention have the formula indicated above wherein **W** is quinolyl, or quinolyl substituted with halogen,  
30 alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms.

In a still more preferred embodiment, compounds of the present invention have the formula indicated above wherein **W** is quinolyl, or quinolyl substituted with halogen, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, **X** is methylene, **Q** is -O-, and **Y** is phenyl.

The most preferred compounds of the present invention are selected from the group consisting of

- [cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]iminoxyacetic acid,  
[cyclohexyl-(4-(2-quinolyl-methoxy)phenyl)methyl]-2-iminoxypropionic acid,  
5 (R)-[Cyclohexyl-(4-(2-quinolyl-methoxy)phenyl)methyl]-2-iminoxypropionic acid,  
(S)-[cyclohexyl-(4-(2-quinolyl-methoxy)phenyl)methyl]-2-iminoxypropionic acid,  
[cyclopentyl-(4-(2-quinolylmethoxy)phenyl)methyl]iminoxyacetic acid,  
[cyclopentyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypropionic acid,  
(R)-[cyclopentyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypropionic acid,  
10 (S)-[cyclopentyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypropionic acid,  
[2-cyclohexyl-1-(4-(2-quinolylmethoxy)phenyl)ethyl]iminoxyacetic acid, and  
[cyclohexyl-(4-(2-benzothiazolylmethoxy)phenyl)methyl]iminoxy acetic acid,  
or a pharmaceutically acceptable salt thereof.

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#### Lipoxygenase Inhibition Determination

Inhibition of leukotriene biosynthesis was evaluated in an assay involving calcium ionophore-induced LTB<sub>4</sub> expressed in human polymorphonuclear leukocytes (PMNL). Human PMNL isolated from heparinized (20 USP units/mL) venous blood (25 mL) obtained from healthy volunteers was layered over an equal  
20 volume of Ficoll-Hypaque Mono-Poly Resolving Medium (ICN Flow, Costa Mesa, CA) and centrifugated at 400 x g for 40 min at 20 °C. The PMNL was collected, erythrocytes lysed and washed 2x and suspended at 1.0 x 10<sup>7</sup> cells/mL in Earle's balanced salt solution with 17 mM Earle's HEPES. Aliquots of the cell suspension were preincubated with test compounds dissolved in DMSO (final concentration  
25 <2%) for 15 min. and stimulated with calcium ionophore (final concentration 8.3 μM) for 10 min. at 37 °C. Incubations were stopped with the addition of two volumes of ice-cold methanol followed by centrifuging the cell suspensions at 4°C for 10 min at 450 x g. The amount of LTB<sub>4</sub> in the methanol extract was analyzed by enzyme-linked immunoassay or by HPLC analysis.

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The compounds of this invention inhibit leukotriene biosynthesis as shown by the data for representative examples in Table 1.

**Table 1**  
*In Vitro* Inhibitory Potencies Against 5-Lipoxygenase from Stimulated LTB<sub>4</sub>  
Formation in Human Polymorphonuclear Leukocytes

Example	IC <sub>50</sub> (μM)
1	0.021
2	0.004
6	0.032
12	0.055
14	0.004
15	0.006
26	0.005
27	0.008
28	0.005
30	0.170
31	0.025
32	0.170
33	0.015
34	0.470
35	0.070
36	0.050
37	0.006
40	0.017
42	< 0.1
43	< 0.1
44	<0.1
45	<0.1
48	<0.1
49	<0.1
50	<0.1
51	<0.1
55	0.030
57	<0.1
58	<0.1
62	0.036



Inhibition of the biosynthesis of leukotrienes *in vivo* after oral administration of compound was determined using a rat peritoneal anaphylaxis model in a similar manner as that described by Young and coworkers (Young, P. R.; Dyer, R.D.; Carter, G. W. Fed. Proc., Fed. Am. Soc. Exp. Biol. 1985, 44, 1185). In this model rats were injected intraperitoneally (ip) with rabbit antibody to bovine serum albumin (BSA) and three hours later injected ip with BSA to induce an antigen-antibody response. Rats were sacrificed 15 minutes after this challenge and the peritoneal fluids were collected and analyzed for leukotriene levels. Test compounds were administered by gavage one hour prior to the antigen challenge. Percent inhibition values were determined by comparing the treatment group to the mean of the control group.

**Table 2**  
*In Vivo* Leukotriene Inhibition in Rat Peritoneal Anaphylaxis Model

Example	% Inhibition (dose) or ED <sub>50</sub>
1	82% at 30 $\mu$ mol/kg
2	1.2 mg/kg
19	81% at 30 $\mu$ mol/kg
27	0.7 mg/kg

Pleural inflammation was induced in male rats following the method of Rao et al (Rao, T. S., Currie, J. L., Shaffer, A. F., Isakson, P. C., (1993) Evaluation of 5-lipoxygenase Inhibitors, Zileuton, A-78773 and ICI D-2138 in an Ionophore (A-23187) Induced Pleural Inflammation Model in the Rat. Life Sciences, 53: 147). Rats were dosed with experimental compounds in 0.2% methocel one hour prior to the intrapleural injection of the calcium ionophore, A23187. The rats were lightly anesthetized with Pentrane (Abbott Laboratories) and injected intrapleurally with 0.5 ml of 2% ethanol in injectable saline (Abbott Laboratories) containing 20  $\mu$ g of A23187 (Cal BioChem-Novabiochem). Thirty minutes later the animals were euthanized and the pleural cavities lavaged with ice cold saline (Abbott Laboratories). The lavage fluid was then added to ice cold methanol (final methanol concentration 30%) to lyse cells and precipitate protein. Eicosanoids were determined by enzyme immunoassay by standard methods.

**Table 3**  
*In Vivo* Leukotriene Inhibition in Rat Pleural Inflammation

Example	% Inhibition (dose) or ED <sub>50</sub>
2	89% at 30 $\mu$ mol/kg
45	1.2 mg/kg
48	2.0 mg/kg

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### Pharmaceutical Compositions

The present invention also provides pharmaceutical compositions which comprise compounds of the present invention formulated together with one or more non-toxic pharmaceutically acceptable carriers. The pharmaceutical compositions may be specially formulated for oral administration in solid or liquid form, for parenteral injection, or for rectal administration.

The pharmaceutical compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, or as an oral or nasal spray. The term "parenteral" administration as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Pharmaceutical compositions of this invention for parenteral injection comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservative, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form

may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of the drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

5 The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric  
10 substances and waxes.

The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the  
15 active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethyl formamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and  
20 sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

25 Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, and tragacanth, and mixtures thereof.

30 Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at room temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and the phosphatidyl cholines (lecithins), both natural and synthetic.

Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 et seq.

Dosage forms for topical administration of a compound of this invention include powders, sprays, ointments and inhalants. The active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives, buffers, or propellants which may be required. Ophthalmic formulations, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

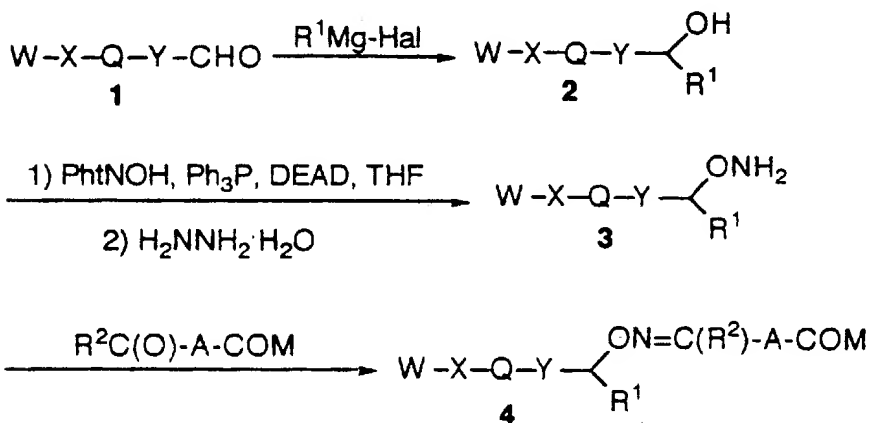
Actual dosage levels of active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active compound(s) that is effective to achieve the desired therapeutic response for a particular patient, compositions, and mode of administration. The selected dosage level will depend upon the activity of the particular compound, the route of administration, the severity of the condition being treated, and the condition and prior medical history of the patient being treated. However, it is within the skill of the art to start doses of the compound at levels lower than required for to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

Generally dosage levels of about 1 to about 50, more preferably of about 5 to about 20 mg of active compound per kilogram of body weight per day are administered orally to a mammalian patient. If desired, the effective daily dose may be divided into multiple doses for purposes of administration, e.g. two to four separate doses per day.

### Preparation of Compounds of this Invention

The oxime carboxylate compounds of this invention can be prepared by several procedures and representative methods are outlined in Scheme 1. Scheme 1 describes a general procedure involving treatment of the requisite aldehyde **1** (where W, X, Q and Y are groups as previously defined) with a Grignard intermediate (where Hal is halogen and R<sup>1</sup> is as previously described) to provide the hydroxy intermediate **2**. This intermediate is treated with N-hydroxyphthalimide, triphenylphosphine and diethylazodicarboxylate (DEAD) to form a N-phthaloyl intermediate which is subsequently treated hydrazine hydrate to provide the desired O-alkylhydroxylamine intermediate **3**. This intermediate is reacted with an oxoalkylcarboxylate (where R<sup>2</sup> and A are groups as defined previously) to provide the desired compounds.

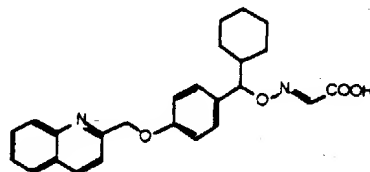
Scheme 1



15

The foregoing may be better understood by reference to the following examples which are provided for illustration and not intended to limit the scope of the inventive concept. The following abbreviations are used: THF for tetrahydrofuran, *n*-BuLi for *n*-butyllithium, DCC for dicyclohexyl carbodiimide, DEAD for diethyl azodicarboxylate, DMF for *N,N*-dimethylformamide, DIAD for diisopropyl azodicarboxylate, CDCl<sub>3</sub> for deuteriochloroform, DMSO-d<sub>6</sub> for deuterodimethylsulfoxide, DIBAL for diisobutylaluminum hydride, LAH for lithium aluminum hydride, LDA for lithium diisopropylamide and TDA-1 for tris[2-(2-methoxyethoxy)ethyl]amine.

25

**Example 1**Preparation of [Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]iminooxyacetic acid.5    Step 1: 4-(2-quinolylmethoxy)benzaldehyde.

To a solution of 4-hydroxybenzaldehyde (3.66 g, 30 mmol) and potassium carbonate (8.24 g, 60 mmol) in DMF (75 mL) was added 2-chloromethylquinoline hydrochloride (6.42 g, 30 mmol), and the resulting solution was stirred at ambient temperature for 16 hours. The reaction mixture was then poured into water (100 mL) and extracted with ethyl acetate (100 mL). The extract was dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with 2:1 hexane-ethyl acetate to afford 4-(2-quinolylmethoxy)benzaldehyde (5.8 g, 74%) as a crystalline compound.

15    Step 2: {Cyclohexyl-[4-(2-quinolylmethoxy)phenyl]}methanol.

To a solution of 4-(2-quinolylmethoxy)benzaldehyde (2.63 g, 10 mmol), prepared as in step 1, in THF (50 mL) at -78 °C was added cyclohexylmagnesium chloride (10 mL of a 2 M solution in THF, 20 mmol). The resulting mixture was stirred at ambient temperature for 12 hours and then quenched with aqueous saturated NH<sub>4</sub>Cl (25 mL) and the THF was removed *in vacuo*. To the residue was added water (50 mL) and the product was extracted with ethyl acetate (100 mL). The extract was dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by column chromatography eluting with 9:1 methylene chloride-ethyl acetate to afford 3.3 g (94%) of {Cyclohexyl-[4-(2-quinolylmethoxy)phenyl]}methanol.

25    Step 3: N-Phthaloyl-O-{cyclohexyl-[4-(2-quinolylmethoxy)phenyl]}methylhydroxylamine.

To a mixture of the {Cyclohexyl-[4-(2-quinolylmethoxy)phenyl]}methanol, prepared in step 2, triphenylphosphine (3.93 g, 15 mmol) and N-hydroxyphthalimide (1.55 g, 9.5 mmol) in THF (100 mL) was added dropwise a solution of DEAD (2.4 mL; 15 mmol) in THF (15 mL). The mixture was then stirred at ambient temperature for 14 hours, concentrated *in vacuo*, and the residue obtained was chromatographed

on silica gel eluting with 2:1 hexane-ethyl acetate to provide *N*-Phthaloyl-*O*-{cyclohexyl-[4-(2-quinolylmethoxy)phenyl]}methylhydroxylamine as an oil (5.0 g).

Step 4: *O*-{Cyclohexyl-[4-(2-quinolylmethoxy)phenyl]}methylhydroxylamine.

5 A solution of the *N*-Phthaloyl-*O*-{cyclohexyl-[4-(2-quinolylmethoxy)phenyl]}methylhydroxylamine prepared in step 3 and hydrazine hydrate (1.5 mL, 30 mmol) in 1:1 ethanol-methylene chloride (80 mL) was refluxed for 30 minutes and then cooled to ambient temperature. 10% Sodium carbonate (50 mL) was added, and the mixture was extracted with ethyl acetate (120 mL). The  
10 extract was washed with water (2 x 50 mL) and brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo* to provide 3.11 g of *O*-{Cyclohexyl-[4-(2-quinolylmethoxy)phenyl]}methylhydroxylamine.

Step 5: {Cyclohexyl-[4-(2-quinolylmethoxy)phenyl]methyl}-iminoxyacetic acid.

15 A mixture of the *O*-{Cyclohexyl-[4-(2-quinolylmethoxy)phenyl]}methylhydroxylamine from Step 4 (543 mg, 1.5 mmol), glyoxylic acid hydrate (140 mg, 1.5 mmol), acetic acid (0.09 mL, 1.5 mmol) and sodium acetate trihydrate (207 mg, 1.5 mmol) in methanol (25 mL)-dioxane (10 mL)-water (5 mL) was stirred at ambient temperature for 48 hours. The organics were  
20 removed *in vacuo*, and water (25 mL) and 1*N* sodium hydroxide (4 mL) were added. The insoluble material was extracted with ethyl ether (2 x 25 mL), and the aqueous solution was acidified to pH 3 with 10% citric acid. The precipitated solid was filtered and recrystallized from ethyl acetate-hexane to afford 400 mg (64%) of  
25 {Cyclohexyl-[4-(2-quinolylmethoxy)phenyl]methyl}-iminoxyacetic acid. m.p. 199-200 °C. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 1.1 (m, 5H), 1.3 (m, 1H), 1.7 (m, 4H), 1.9 (m, 1H), 4.9 (d, *J* = 7 Hz, 1H), 5.38 (s, 2H), 7.05 (d, *J* = 9 Hz, 2H), 7.2 (d, *J* = 9 Hz, 2H), 7.56 (s, 1H), 7.62 (t, *J* = 8 Hz, 1H), 7.7 (d, *J* = 8 Hz, 1H), 7.8 (m, 1H), 8.0 (t, *J* = 8 Hz, 2H), 8.43 (d, *J* = 8 Hz, 1H). MS (DCI/NH<sub>3</sub>) *m/e* 419 (M+H)<sup>+</sup>. IR (KBr): 3450, 1700, 1605 cm<sup>-1</sup>. Analysis calcd. for C<sub>25</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>: C, 71.75; H, 6.26; N, 6.69; Found: C, 71.42; H, 6.25; N, 6.45.  
30



### Example 2

#### Preparation of [Cyclohexyl-[4-(2-quinolylmethoxy)phenyl]methyl]-2-iminoxy propionic acid

#### Step 1: Cyclohexyl-[4-(2-quinolylmethoxy)phenyl]methyl}-iminoxy-2-propionic acid methyl ester.

A mixture of *O*-{cyclohexyl-[4-(2-quinolylmethoxy)phenyl]methyl}-hydroxylamine (543 mg, 1.5 mmol), prepared as in Example 1, step 4, methyl pyruvate (0.14 mL, 1.5 mmol) and acetic acid (0.09 mL, 1.5 mmol) in methanol (25 mL)-dioxane (10 mL) and water (5 mL) was stirred at ambient temperature for 24 hours. After the organic solvents were removed *in vacuo*, water (25 mL) was added to the residue. The resulting mixture was extracted with ethyl acetate, dried with MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with 3:1 hexane-ethyl acetate to afford 300 mg of Cyclohexyl-[4-(2-quinolylmethoxy)phenyl]methyl}-iminoxy-2-propionic acid methyl ester as an oil.

#### Step 2: Cyclohexyl-[4-(2-quinolylmethoxy)phenyl]methyl}-iminoxy-2-propionic acid.

To a solution of the Cyclohexyl-[4-(2-quinolylmethoxy)phenyl]methyl}-iminoxy-2-propionic acid methyl ester from step 1 in 2:1 methanol-dioxane (30 mL) was added 1N sodium hydroxide (2 mL), and the resulting mixture was refluxed at 50 °C for 30 minutes. The organics were then removed *in vacuo*, and water (25 mL) was added to the residue. The aqueous solution was washed with ethyl ether (25 mL) and then acidified with 50% citric acid. The solid obtained was filtered, dried *in vacuo* and recrystallized from ethyl acetate-hexane to provide 210 mg of Cyclohexyl-[4-(2-quinolylmethoxy)phenyl]methyl}-iminoxy-2-propionic acid as a mixture of *E* and *Z* isomers. m.p. 185-186 °C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.1 (m, 5H), 1.33 (m, 1H), 1.7 (m, 4H), 1.9 (m, 1H), 2.0 (s, 3H), 4.92 (d, J = 7Hz, 1H), 5.36 (s, 2H), 7.03 (d, J = 9 Hz, 2H), 7.2 (d, J = 9Hz, 2H), 7.62 (m, 1H), 7.7 (d, J = 9 Hz, 1H), 7.8 (m, 1H), 8.0 (t, J = 9 Hz, 2H), 8.43 (d, J = 9 Hz, 1H), 12.95 (br. s, 1H). MS (DCI/NH<sub>3</sub>) m/e 433 (M+H)<sup>+</sup>. IR (CDCl<sub>3</sub>): 3420, 1750, 1610 cm<sup>-1</sup>. Analysis calcd. for C<sub>26</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub>: C, 72.20; H, 6.53; N, 6.48. Found: C, 71.99; H, 6.42; N, 6.21.

**Example 3**Preparation of [Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-4-iminoxy pentanoic acid

The title compound was prepared according to the procedure of Example 1, except substituting levulinic acid (4-oxo-pentanoic acid) for glyoxylic acid. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.1 (m, 5H), 1.35 (m, 1H), 1.6 (m, 4H), 1.8 (m, 5H), 2.3 (s, 3H), 4.68 (d, J = 7 Hz, 1H), 5.33 (s, 2H), 7.0 (d, J = 9 Hz, 2H), 7.13 (d, J = 9 Hz, 2H), 7.53 (m, 1H), 7.68 (d, J = 9 Hz, 1H), 7.8 (m, 1H), 8.0 (t, J = 9 Hz, 2H), 8.43 (d, J = 9 Hz, 1H). MS (DCI/NH<sub>3</sub>) m/e 461 (M+H)<sup>+</sup>. IR (CDCl<sub>3</sub>): 3480, 1710 with shoulder 1740, 1605 cm<sup>-1</sup>. Analysis calcd for C<sub>28</sub>H<sub>32</sub>N<sub>2</sub>O<sub>4</sub> · H<sub>2</sub>O: C, 70.27; H, 7.16; N, 5.85. Found: C, 70.81; H, 7.17; N, 6.18.

**Example 4**Preparation of [Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxy-3-(4-hydroxyphenyl)propionic acid

The title compound was prepared according to the procedure of Example 1, except substituting 3-(4-hydroxyphenyl)-2-oxo-propionic acid for glyoxylic acid. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.1 (m, 5H), 1.35 (m, 1H), 1.6 (m, 4H), 1.8 (m, 1H), 7.73 (two d, J = 12 Hz, 2H), 4.62 and 4.85 (two d, 1:4, J = 7 Hz, 1H), 5.35 (two s, 4:1, 2H), 6.56 (two d, 1:4, J = 9 Hz, 2H), 7.0 (m, 6H), 7.65 (m, 2H), 7.8 (m, 1H), 8.0 (t, J = 8 Hz, 2H), 8.43 (d, J = 8 Hz, 1H), 9.15 (br. s, 1H). MS (DCI/NH<sub>3</sub>) m/e 525 (M+H)<sup>+</sup>. IR (KBr): 3440, 1710, 1610 cm<sup>-1</sup>.

**Example 5**Preparation of [Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxy-3-phenylpropionic acid

The desired material was prepared according to the procedure of Example 1, except substituting 2-oxo-3-(phenyl)propionic acid for glyoxylic acid. m.p. 92-95 °C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.0 (m, 5H), 1.3 (m, 1H), 1.6 (m, 5H), 3.85 (m, 2H), 4.62 and 4.84 (two d, 5:1, J = 7 Hz, 1H), 5.35 (two s, 5:1, 2H), 7.0 (m, 5H), 7.25 (m, 3H), 7.65 (m, 2H), 7.8 (m, 1H), 8.0 (t, J = 8 Hz, 2H), 8.43 (d, J = 8 Hz, 1H). MS (DCI/NH<sub>3</sub>) m/e 509 (M+H)<sup>+</sup>, 1036 (2M+H+NH<sub>3</sub>)<sup>+</sup>. IR (CDCl<sub>3</sub>): 3430, 1750, 1610 cm<sup>-1</sup>. Analysis calcd. for C<sub>32</sub>H<sub>32</sub>N<sub>2</sub>O<sub>4</sub>: C, 72.98; H, 6.51; N, 5.32. Found C, 72.87; H, 5.84; N, 4.97.

**Example 6**Preparation of *O*-[Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-4-carboxybenzaldehyde

The desired material was prepared according to the procedure of Example 1, except substituting 4-carboxybenzaldehyde for glyoxylic acid. m.p. 174-175 °C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.1 (m, 5H), 1.35 (m, 1H), 1.7 (m, 4H), 1.95 (m, 1H), 4.9 (d, J = 7 Hz, 1H), 5.35 (s, 2H), 7.04 (d, J = 8 Hz, 2H), 7.22 (d, J = 8 Hz, 2H), 7.65 (m, 4H), 7.8 (m, 1H), 7.9 (d, J = 8 Hz, 2H), 8.0 (m, 2H), 8.36 (s, 1H), 8.41 (d, J = 8 Hz, 1H), 13.05 (broad s, 1H). MS (DCI/NH<sub>3</sub>) m/e 495 (M+H)<sup>+</sup>. IR (KBr): 3440, 1695, 1600 cm<sup>-1</sup>. Analysis calcd. for C<sub>31</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub>: C, 75.28; H, 6.11; N, 5.66. Found: C, 74.99; H, 6.09; N, 5.62.

**Example 7**Preparation of [Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-3-iminoxy-(2,2-dimethyl)propionic acid

The desired material was prepared according to the procedure of Example 2, except substituting the monoaldehyde-monomethyl ester of (2,2-dimethyl)malonic acid for methyl pyruvate. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 0.9 (m, 1H), 1.07 (m + two s, 9H), 1.3 (m, 2H), 1.62 (m, 4H), 1.85 (m, 1H), 4.67 (d, J = 7 Hz, 1H), 5.33 (s, 2H), 7.0 (d, J = 9 Hz, 2H), 7.13 (d, J = 9 Hz, 2H), 7.62 (m, 2H), 7.69 (d, J = 8 Hz, 1H), 8.0 (t, J = 8 Hz, 2H), 8.42 (d, J = 8 Hz, 1H). MS (DCI/NH<sub>3</sub>) m/e 461 (M+H)<sup>+</sup>. IR (CDCl<sub>3</sub>): 3400, 1670, 1600 cm<sup>-1</sup>.

**Example 8**Preparation of [Cyclopentyl-(4-(2-quinolylmethoxy)phenyl)methyl]iminoxy acetic acid

The desired material was prepared according to the procedure of Example 1, except substituting cyclopentyl magnesium chloride for cyclohexylmagnesium chloride. m.p. 187-188 °C (after crystallization from CH<sub>2</sub>Cl<sub>2</sub>-ethyl ether-hexane). <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.12 (m, 1H), 1.3 (m, 1H), 1.5 (m, 5H), 1.8 (m, 1H), 2.32 (m, 1H), 4.92 (d, J = 7 Hz, 1H), 5.36 (s, 2H), 7.04 (d, J = 9 Hz, 2H), 7.26 (d, J = 9 Hz, 2H), 7.54 (s, 1H), 7.61 (m, 1H), 7.7 (d, J = 8 Hz, 1H), 7.8 (m, 1H), 8.0 (t, J = 8 Hz, 2H), 8.42 (d, J = 8 Hz, 1H). MS (DCI/NH<sub>3</sub>) m/e 405 (M+H)<sup>+</sup>. IR (KBr): 3450, 1700, 1610 cm<sup>-1</sup>. Analysis calcd. for C<sub>24</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>: C, 71.27; H, 5.98; N, 6.93. Found: C, 70.99; H, 6.08; N, 6.87.

**Example 9**Preparation of [Cyclopentyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxy propionic acid

The desired material was prepared according to the procedure of Example 2, except substituting cyclopentyl magnesium chloride for cyclohexyl magnesium chloride. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.18 (m, 1H), 1.3 (m, 1H), 1.5 (m, 5H), 1.75 (m, 1H), 1.96 (s, 3H), 2.33 (m, 1H), 4.95 (d, J = 7 Hz, 1H), 5.36 (s, 2H), 7.03 (d, J = 9 Hz, 2H), 7.25 (d, J = 9 Hz, 2H), 7.63 (m, 1H), 7.7 (d, J = 8 Hz, 1H), 7.8 (m, 1H), 8.0 (t, J = 8 Hz, 2H), 8.42 (d, J = 8 Hz, 1H), 12.9 (broad s, 1H). MS (DCI/NH<sub>3</sub>) m/e 419 (M+H)<sup>+</sup>. IR (CDCl<sub>3</sub>): 3400, 1760, 1705 cm<sup>-1</sup>. Analysis calcd. for C<sub>25</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>: C, 71.75; H, 6.26; N, 6.69. Found: C, 71.76; H, 6.04; N, 6.60.

**Example 10**Preparation of [1,2,3,4-Tetrahydro-6-(2-quinolylmethoxy)naphth-1-yl]iminoxy acetic acid.Step 1: 6-hydroxytetralone.

A mixture of 6-methoxytetralone (8.8 g, 50 mmol) and 48% hydrobromic acid (25 mL) in acetic acid (25 mL) was refluxed at 125 °C for 3 hours. The mixture was then poured into ice/water and extracted with ethyl acetate (125 mL). The extract was washed with water and brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. To the residue was added CH<sub>2</sub>Cl<sub>2</sub> (25 mL), and the suspension was cooled at 0 °C for 2 hours. The solid was filtered and washed with cold CH<sub>2</sub>Cl<sub>2</sub> to afford 5.8 g of 6-hydroxytetralone.

Step 2: 3,4-Dihydro-6-(2-quinolylmethoxy)-1(2H)-naphthalenone.

To a mixture of 6-hydroxytetralone, prepared as in step 1, (2.43 g, 15 mmol) and potassium carbonate (2.76 g, 20 mmol) in DMF (65 mL) was added chloromethylquinoline hydrochloride (3.42 g, 16 mmol), and the resulting mixture was stirred at ambient temperature for 24 hours. The reaction mixture was then poured into water (100 mL) and extracted with ethyl acetate (100 mL). The extract was dried with MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with 5:1 methylene chloride-ethyl acetate to provide 2.3 g 3,4-Dihydro-6-(2-quinolylmethoxy)-1(2H)-naphthalenone.

Step 3: 1,2,3,4-Tetrahydro-6-(2-quinolylmethoxy)-1-naphthalenol.

A mixture of 3,4-dihydro-6-(2-quinolylmethoxy)-1(2H)-naphthalenone (1.82 g, 6 mmol), prepared as in step 2, and sodium borohydride (230 mg, 6 mmol) in ethanol (15 mL) was refluxed for 30 minutes. The reaction was allowed to warm to ambient temperature and was then quenched with saturated  $\text{NH}_4\text{Cl}$ . Extraction with ethyl acetate and purification on a silica gel column eluting with 9:1  $\text{CH}_2\text{Cl}_2$ -ethyl acetate afforded 1.79 g of 1,2,3,4-tetrahydro-6-(2-quinolylmethoxy)-1-naphthalenol.

Step 4: N-phthaloyl-O-(1,2,3,4-tetrahydro-6-(2-quinolyl-methoxy)-1-naphthyl)hydroxylamine.

To a solution of 1,2,3,4-tetrahydro-6-(2-quinolylmethoxy)-1-naphthalenol (1.41 g, 4.6 mmol), prepared as in step 3, *N*-hydroxyphthalimide (750 mg, 4.6 mmol) and triphenylphosphine (1.83 g, 7 mmol) in THF (90 mL) at ambient temperature was added dropwise a solution of DEAD (1.12 mL, 7 mmol) in THF (10 mL). The resulting solution was stirred at ambient temperature for 10 hours and then concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with 19:1  $\text{CH}_2\text{Cl}_2$ -ethyl acetate to afford 1.85 g of *N*-phthaloyl-O-(1,2,3,4-tetrahydro-6-(2-quinolyl-methoxy)-1-naphthyl)hydroxylamine.

Step 5: O-[1,2,3,4-tetrahydro-6-(2-quinolylmethoxy)-1-naphthyl]hydroxylamine.

A mixture of the *N*-phthaloyl-O-(1,2,3,4-tetrahydro-6-(2-quinolyl-methoxy)-1-naphthyl)hydroxylamine prepared in step 4 and hydrazine hydrate (0.5 mL, 10 mmol) in 2:1 ethanol-dioxane (45 mL) was refluxed for 30 minutes and then was allowed to cool to ambient temperature. 10% Sodium carbonate (10 mL) was added and the resulting mixture was extracted with ethyl acetate (100 mL). The extract was washed with water and brine, dried over  $\text{MgSO}_4$  and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with ethyl acetate to afford 510 mg of O-[1,2,3,4-tetrahydro-6-(2-quinolylmethoxy)-1-naphthyl]hydroxylamine.

Step 6: [1,2,3,4-tetrahydro-6-(2-quinolylmethoxy)-1-naphthyl]liminoxyacetic acid.

A solution of the O-[1,2,3,4-tetrahydro-6-(2-quinolylmethoxy)-1-naphthyl]hydroxylamine prepared in Step 5 (260 mg, 0.8 mmol), glyoxylic acid hydrate (184 mg, 2 mmol), acetic acid (0.06 mL, 1 mmol) and sodium acetate (276 mg, 2 mmol) in methanol (30 mL)-dioxane (10 mL)-water (5 mL) was stirred at ambient temperature for 12 hours, and then concentrated *in vacuo*. To the residue was added 1N NaOH (3 mL) and water (10 mL), and the mixture was washed with

ethyl ether (10 mL). The aqueous solution was acidified with 10% citric acid to pH 3 and the precipitated solid was filtered. Recrystallization from ethyl ether-hexane provided 300 mg of [1,2,3,4-tetrahydro-6-(2-quinolylmethoxy)-1-naphthyl]iminoxyacetic acid. m.p. 99-101 °C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.7 (m, 2H), 1.87 (m, 1H), 2.12 (m, 1H), 2.7 (m, 2H), 5.25 (t, J = 2 Hz, 1H), 5.38 (s, 2H), 6.9 (m, 2H), 7.25 (d, J = 9 Hz, 1H), 7.53 (s, 1H), 7.65 (m, 2H), 7.8 (m, 1H), 8.0 (t, J = 8 Hz, 2H), 8.4 (d, J = 8 Hz, 1H). MS (DCI/NH<sub>3</sub>) m/e 377 (M+H)<sup>+</sup>. IR (KBr): 3450, 1710, 1605 cm<sup>-1</sup>. Analysis calcd. for C<sub>22</sub>H<sub>20</sub>N<sub>2</sub>O<sub>4</sub>: C, 70.20; H, 5.36; N, 7.44. Found: C, 69.47; H, 5.48; N, 7.44.

### Example 11

#### Preparation of [1,2,3,4-Tetrahydro-6-(2-quinolylmethoxy)naphth-1-yl]-2-iminoxypropionic acid

##### Step 1: [1,2,3,4-Tetrahydro-6-(2-quinolylmethoxy)naphth-1-yl]-2-iminoxypropionic acid methyl ester.

A mixture O-(1,2,3,4-tetrahydro-6-(2-quinolylmethoxy)naphth-1-yl)hydroxylamine (160 mg, 0.5 mmol), prepared as in Example 10, step 5, methyl pyruvate (104 mg, 1 mmol) and acetic acid (0.05 mL, 1 mmol) in methanol (25 mL)-dioxane (10 mL) was stirred at ambient temperature for 24 hours and then concentrated *in vacuo*. To the residue was added water (20 mL), and the product was extracted with ethyl acetate (75 mL). The extract was concentrated *in vacuo* and the residue was chromatographed on silica gel eluting with 3:1 hexane-ethyl acetate to afford 200 mg of 2-(1,2,3,4-tetrahydro-6-(2-quinolylmethoxy)-1-naphthyl)iminoxypropionic acid methyl ester.

##### Step 2: [1,2,3,4-Tetrahydro-6-(2-quinolylmethoxy)naphth-1-yl]-2-iminoxypropionic acid.

To a solution of the 2-(1,2,3,4-tetrahydro-6-(2-quinolylmethoxy)-1-naphthyl)iminoxypropionic acid methyl ester prepared in step 1 in methanol (25 mL) was added 1N NaOH (2 mL), and the resulting mixture was refluxed at 50 °C for 30 minutes. The methanol was removed *in vacuo*, and 25 mL of water was added to the residue. The resulting aqueous solution was washed with ethyl ether (25 mL) and acidified to pH 3 with 10% citric acid. The precipitated solid was filtered and recrystallized from ethyl ether-hexane to provide 120 mg of [1,2,3,4-Tetrahydro-6-(2-quinolylmethoxy)naphth-1-yl]-2-iminoxypropionic acid. m.p. 83-85 °C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.7 (m, 2H), 1.87 (m + s, 4H), 2.1 (m, 1H), 2.7 (m,

2H), 5.24 (t,  $J = 2$  Hz, 1H), 5.37 (s, 2H), 6.9 (m, 2H), 7.3 (d,  $J = 9$  Hz, 1H), 7.63 (m, 2H), 7.8 (m, 1H), 8.0 (t,  $J = 8$  Hz, 2H), 8.42 (d,  $J = 8$  Hz, 1H). MS (DCI/ $\text{NH}_3$ )  $m/e$  391 ( $\text{M}+\text{H}$ )<sup>+</sup>. IR ( $\text{CDCl}_3$ ): 3420, 1760, 1600  $\text{cm}^{-1}$ . Analysis calcd. for  $\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_4$ : C, 70.75; H, 5.68; N, 7.17. Found: C, 70.20; H, 5.47; N, 7.00.

5

### Example 12

Preparation of [4-(4-Chlorophenyl)-1-(4-(2-quinolylmethoxy)phenyl)butyl]liminooxyacetic acid

Step 1: 4-(4-Chlorophenyl)-1-[4-(2-quinolylmethoxy)phenyl]butan-1-ol.

10 A suspension of magnesium turnings (264 mg, 11 mmol) in THF (15 mL) was activated with iodine crystals. A few drops of 1-bromo-4-(4-chlorophenyl)butane was added, and the mixture was warmed until the exothermic Grignard reaction commenced. The remaining 1-bromo-4-(4-chlorophenyl)butane (2.33 g, 10 mmol) was added dropwise at a rate sufficient to maintain a gentle reflux.

15 After addition was complete, the mixture was heated at reflux for 30 minutes and then cooled to  $-78^\circ\text{C}$ . The resulting cold solution of was slowly cannulated into a cold solution of 4-(2-quinolylmethoxy)benzaldehyde (2.63 g, 10 mmol) in THF (25 mL), and the mixture was allowed to stand at ambient temperature for 12 hours. The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (20 mL) and extracted with

20 ethyl acetate (100 mL). The combined organic extracts were dried over  $\text{MgSO}_4$  and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with 6:1 methylene chloride-ethyl acetate to afford 2.0 g of 4-(4-Chlorophenyl)-1-[4-(2-quinolylmethoxy)phenyl]butan-1-ol.

25 Step 2: *N*-phthaloyl-*O*-(4-(4-chlorophenyl)-1-[4-(2-quinolyl-methoxy)phenyl]but-1-yl)hydroxylamine.

To a solution of 4-(4-Chlorophenyl)-1-[4-(2-quinolylmethoxy)phenyl]butan-1-ol (630 mg, 1.5 mmol), prepared as in step 1, triphenylphosphine (393 mg, 1.5 mmol) and *N*-hydroxyphthalimide (245 mg, 1.5 mmol) in THF (120 mL) was added

30 dropwise a solution of DIAD (0.3 mL, 1.5 mmol) in THF (10 mL). The resulting mixture was stirred at ambient temperature for 14 hours and then concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with 3:1 hexane-ethyl acetate to provide 1.0 g of *N*-phthaloyl-*O*-(4-(4-chlorophenyl)-1-[4-(2-quinolyl-methoxy)phenyl]but-1-yl)hydroxylamine.

35

Step 3: *O*-{4-(4-chlorophenyl)-1-[4-(2-quinolylmethoxy)-phenyl]but-1-yl}hydroxylamine.

A solution of the *N*-phthaloyl-*O*-(4-(4-chlorophenyl)-1-(4-(2-quinolylmethoxy)phenyl)but-1-yl)hydroxylamine prepared in step 2 in 2:1 ethanol-methylene chloride (60 mL) was treated with hydrazine hydrate (0.24 mL, 5.0 mmol) and refluxed for 30 minutes. Then 10% sodium carbonate (20 mL) was added and the resulting mixture was extracted with ethyl ether (100 mL). The ether extract was washed with water (2x50 mL) and brine, dried over MgSO<sub>4</sub> and concentrated *in vacuo* to provide 650 mg of *O*-{4-(4-chlorophenyl)-1-[4-(2-quinolylmethoxy)-phenyl]but-1-yl}hydroxylamine.

Step 4: {4-(4-chlorophenyl)-1-[4-(2-quinolylmethoxy)phenyl]-butyl}iminooxyacetic acid.

A solution of *O*-{4-(4-chlorophenyl)-1-[4-(2-quinolylmethoxy)-phenyl]but-1-yl}hydroxylamine in 1:5 water methanol (60 mL) was treated with glyoxylic acid hydrate (184 mg, 2 mmol) and acetic acid (0.12 mL; 2 mmol) for 18 hours at ambient temperature. The methanol was then removed *in vacuo* and the residue extracted with ethyl acetate. Purification on silica gel eluting with 8:1 methylene chloride-ethanol afforded 600 mg (80%) of {4-(4-chlorophenyl)-1-[4-(2-quinolylmethoxy)phenyl]-butyl}iminooxyacetic acid as an amorphous solid. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.5 (m, 1H), 1.65 (m, 2H), 1.9 (m, 1H), 2.6 (t, J = 7 Hz, 2H), 5.1 (t, J = 7 Hz, 1H), 5.4 (s, 2H), 7.05 (d, J = 9 Hz, 2H), 7.2 (d, J = 9 Hz, 2H), 7.3 (d, J = 9 Hz, 2H), 7.6 (m, 3H), 7.8 (m, 1H), 8.0 (t, J = 8 Hz, 2H), 8.4 (d, J = 8 Hz, 1H). IR (CDCl<sub>3</sub>): 3450, 1730, 1670, 1610 cm<sup>-1</sup>. MS (DCI/NH<sub>3</sub>) m/e 489 (M+H)<sup>+</sup>.

**Example 13**

Preparation of [2-Cyclohexyl-1-(4-(2-quinolylmethoxy)phenyl)ethyl-1-yl]iminooxyacetic acid

The desired material was prepared according to the procedure of Example 1, except substituting cyclohexylmethylmagnesium bromide for cyclohexylmagnesium chloride. m.p. 180-181 °C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 0.95 (m, 2H), 1.12 (m, 4H), 1.65 (m, 6H), 1.8 (m, 1H), 5.23 (t, J = 7 Hz, 1H), 5.36 (s, 2H), 7.05 (d, J = 9 Hz, 2H), 7.27 (d, J = 9 Hz, 2H), 7.54 (s, 1H), 7.62 (m, 2H), 7.67 (d, J = 8 Hz, 1H), 7.8 (m, 1H), 8.0 (t, J = 8 Hz, 2H), 8.43 (d, J = 8 Hz, 1H). MS (DCI/NH<sub>3</sub>) m/e 433 (M+H)<sup>+</sup>. Analysis calcd. for C<sub>26</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub>: C, 72.19; H, 6.52; N, 6.48. Found: C, 72.03; H, 6.50; N, 6.33.



**Example 14**Preparation of O-[2-Cyclohexyl-1-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]-4-carboxybenzaldoxime

5       The title compound was prepared according to the procedure of Example 1, except substituting cyclohexylmethylmagnesium bromide for cyclohexylmagnesium chloride and substituting 4-carboxybenzaldehyde for glyoxylic acid. m.p. 167-168 °C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 0.95 (m, 2H), 1.15 (m, 4H), 1.6 (m, 4H), 1.73 (m, 2H), 1.87 (m, 1H), 5.23 (t, J = 7 Hz, 1H), 5.46 (s, 2H), 7.05 (d, J = 9 Hz, 2H), 7.32 (d, J = 9 Hz, 2H), 7.63 (m, 4H), 7.79 (m, 1H), 7.93 (d, J = 8 Hz, 2H), 8.0 (t, J = 8 Hz, 2H), 8.31 (s, 1H), 8.41 (d, J = 8 Hz, 1H). MS (DCI/NH<sub>3</sub>) m/e 509 (M+H)<sup>+</sup>. Analysis calcd. for C<sub>32</sub>H<sub>32</sub>N<sub>2</sub>O<sub>4</sub>: C, 74.56; H, 6.34; N, 5.51. Found: C, 74.89; H, 6.25; N, 5.35.

**Example 15**Preparation of [2-Cyclohexyl-1-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]-2-iminoxypropionic acid

15       The title compound was prepared according to the procedure of Example 2, except substituting cyclohexylmethylmagnesium bromide for cyclohexylmagnesium chloride. mp. 152-154 °C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 0.94 (m, 2H), 1.12 (m, 4H), 1.65 (m, 7H), 1.9 (s, 3H), 5.14 (t, J = 7 Hz, 1H), 5.35 (s, 2H), 7.03 d, J = 9 Hz, 2H), 7.22 (d, J = 9 Hz, 2H), 7.65 (m, 2H), 7.79 (m, 1H), 8.02 (t, J = 8 Hz, 2H), 8.42 (d, J = 8 Hz, 1H). MS (DCI/NH<sub>3</sub>) m/e 447 (M+H)<sup>+</sup>. Analysis calcd for C<sub>27</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub>: C, 68.64; H, 6.99; N, 5.93. Found: C, 68.52; H, 6.39; N, 5.76.

**Example 16**Preparation of [2-cyclohexyl-1-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]-4-iminoxypentanoic acid

25       The title compound was prepared according to the procedure of Example 1, except substituting cyclohexylmethylmagnesium bromide for cyclohexylmagnesium chloride and substituting 4-oxopentanoic acid for glyoxylic acid. m.p. 94-96 °C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 0.92 (m, 2H), 1.15 (m, 4H), 1.47 (m, 1H), 1.65 (m, 9H), 2.38 (m, 4H), 4.98 (m, 1H), 5.35 (s, 2H), 7.02 (d, J = 9 Hz, 2H), 7.2 (m, 2H), 7.62 (m, 1H), 7.68 (d, J = 8 Hz, 1H), 7.8 (m, 1H), 8.02 (t, J = 8 Hz, 2H), 8.43 (d, J = 8 Hz, 1H). MS (DCI/NH<sub>3</sub>) m/e 475 (M+H)<sup>+</sup>. Analysis calcd. for C<sub>29</sub>H<sub>34</sub>N<sub>2</sub>O<sub>4</sub>: C, 73.38; H, 7.22; N, 5.83; Found: C, 73.00; H, 7.21; N, 5.83.

**Example 17**Preparation of [cycloheptyl-(4-(2-quinolylmethoxy)phenyl)methyl]liminoxy acetic acid

The title compound was prepared according to the procedure of Example 1, except substituting cycloheptylmagnesium bromide for cyclohexylmagnesium chloride. mp. 184-186 °C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.1 (m, 1H), 1.53 (m, 9H), 1.82 (m, 2H), 1.97 (m, 1H), 4.96 (d, J = 7 Hz, 1H), 5.36 (s, 2H), 7.05 (d, J = 9 Hz, 2H), 7.22 (d, J = 9 Hz, 2H), 7.56 (s, 1H), 7.64 (m, 2H), 7.8 (t, J = 8 Hz, 1H), 8.01 (t, J = 8 Hz, 2H), 8.43 (d, J = 8 Hz, 1H). MS (DCI/NH<sub>3</sub>) m/e 433 (M+H)<sup>+</sup>. Analysis calcd. for C<sub>26</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub>: C, 72.19; H, 6.52; N, 6.47. Found: C, 72.55; H, 6.55; N, 6.42.

**Example 18**Preparation of [2-cyclohexyl-1-(4-(4-thiazolylmethoxy)phenyl)ethyl]liminoxy acetic acidStep 1: 4-(4-thiazolylmethoxy)benzaldehyde.

To a solution of 4-hydroxybenzaldehyde (12.1 g, 100 mmol) and potassium carbonate (41.5 g, 0.30 mole) in DMF (100 mL) was added 4-thiazolylmethyl chloride hydrochloride (17.0 g, 100 mmol), and the resulting mixture was stirred at ambient temperature for 48 hours. The mixture was then poured into brine and filtered to collect the precipitated solid. The solid was washed with water (500 mL) and 10% ethyl ether in hexane and dried *in vacuo* to provide 17.6 g of 4-(4-thiazolylmethoxy)benzaldehyde.

Step 2: 2-cyclohexyl-1-(4-(4-thiazolylmethoxy)phenyl)ethan-1-ol.

A suspension of magnesium turnings (840 mg, 35 g-atom) in THF (25 mL) was activated with iodine crystals. A few drops of cyclohexylmethyl bromide were added, and the mixture was warmed until the exothermic Grignard reaction commenced. The remaining bromide (4.9 mL; 35 mmol) was added dropwise at a rate sufficient to maintain a gentle reflux. The mixture was refluxed for an additional 30 minutes, cooled to -78 °C, and then slowly cannulated to a cold solution of 4-(4-thiazolylmethoxy)benzaldehyde (7.6 g, 35 mmol), prepared as in step 1, in THF (75 mL), and the resulting solution was allowed to stand at ambient temperature for 12 hours. Saturated aqueous NH<sub>4</sub>Cl (50 mL) was added and the mixture was extracted with ethyl acetate (100 mL). The organic layer was washed with water and brine, dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was purified on a silica gel

column eluting with 7:3 hexane-ethyl acetate to provide 900 mg of cyclohexylmethyl-(4-(4-thiazolylmethoxy)phenyl) ketone and 5.4 g of 2-cyclohexyl-1-(4-(4-thiazolylmethoxy)phenyl)ethan-1-ol.

5 Step 3: *N*-phthaloyl-*O*-(2-cyclohexyl-1-(4-(4-thiazolylmethoxy)phenyl)eth-1-yl))hydroxylamine.

To a solution of 2-cyclohexyl-1-(4-(4-thiazolylmethoxy)phenyl)ethan-1-ol (4.75 g, 15 mmol), prepared as in step 2, *N*-hydroxyphthalimide (2.85 g, 17.5 mmol) and triphenylphosphine (5.0 g, 19 mmol) in THF (150 mL) was added  
10 dropwise DEAD (3.75 mL, 19 mmol). The solution was allowed to stir at ambient temperature for 14 hours and then concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with 19:1 methylene chloride-ethyl acetate to provide 3.6 g of *N*-phthaloyl-*O*-(2-cyclohexyl-1-(4-(4-thiazolylmethoxy)phenyl)eth-1-yl))hydroxylamine as an oil.

15 Step 4: *O*-{1-(2-cyclohexyl-1-[4-(4-thiazolylmethoxy)phenyl]ethyl)}hydroxylamine.

A mixture of *N*-phthaloyl-*O*-(2-cyclohexyl-1-(4-(4-thiazolylmethoxy)phenyl)eth-1-yl))hydroxylamine (1.4 g, 2.5 mmol), prepared as in step 3, and hydrazine hydrate (0.3 mL; 6 mmol) in ethanol (50 mL) was refluxed for  
20 30 minutes and then cooled to ambient temperature. The precipitated solid was removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was dissolved in methylene chloride and washed with 10% sodium carbonate, water and brine, over MgSO<sub>4</sub> and concentrated *in vacuo* to provide (0.85 g) of *O*-{1-(2-cyclohexyl-1-[4-(4-thiazolylmethoxy)phenyl]ethyl)}hydroxylamine.

25 Step 5: [2-cyclohexyl-1-(4-(4-thiazolylmethoxy)phenyl)eth-1-yl]iminoxy acetic acid.

A solution of *O*-{1-(2-cyclohexyl-1-[4-(4-thiazolylmethoxy)phenyl]ethyl)}hydroxylamine (664 mg, 2 mmol), prepared as in step 4, glyoxylic acid hydrate (368 mg, 4.00 mmol) and acetic acid (0.12 mL; 2.0 mmol) in methanol (15 mL)-THF (60 mL)-H<sub>2</sub>O (15 mL) was stirred at ambient temperature for 14 hours and then  
30 concentrated *in vacuo*. The precipitated solid was filtered, washed with water and 10% ethyl ether in hexane, and dried *in vacuo* to provide 580 mg of [2-cyclohexyl-1-(4-(4-thiazolylmethoxy)phenyl)eth-1-yl]iminoxy acetic acid as a white solid. m.p. 151-153 °C. <sup>1</sup>H NMR (300 MHz; DMSO-*d*<sub>6</sub>) δ 0.95 (m, 2H), 1.15 (m, 4H), 1.63 (m, 6H), 1.8 (m, 1H), 5.23 (m, 3H), 7.04 (d, *J* = 9 Hz, 2H), 7.26 (d, *J* = 9 Hz,  
35 2H), 7.55 (s, 1H), 7.68 (d, *J* = 2 Hz, 1H), 9.13 (d, *J* = 2 Hz, 1H). MS (DCI/NH<sub>3</sub>)

m/e 389 (M+H)<sup>+</sup>, 406 (M+H+NH<sub>3</sub>)<sup>+</sup>. Analysis calcd. for C<sub>20</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>S: C, 61.83; H, 6.22; N, 7.21. Found: C, 62.26; H, 6.32; N, 7.16.

### Example 19

5 Preparation of O-[2-cyclohexyl-1-(4-(4-thiazolylmethoxy)phenyl)eth-1-yl]-4-carboxybenzaloxime

The title compound was prepared according to the procedure of Example 18, except substituting 4-carboxybenzaldehyde for glyoxylic acid. m.p. 68 °C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 0.95 (m, 2H), 1.22 (m, 4H), 1.73 (m, 7H), 5.32 (m, 10 3H), 7.03 (d, J = 9 Hz, 2H), 7.32 (d, J = 9 Hz, 2H), 7.63 (d, J = 8 Hz, 2H), 7.78 (s, 1H), 7.93 (d, J = 8 Hz, 2H), 8.34 (s, 1H), 9.14 (m, 1H). MS (DCI/NH<sub>3</sub>) m/e 465 (M+H)<sup>+</sup>, 482 (M+H+NH<sub>3</sub>)<sup>+</sup>. Analysis calcd. for C<sub>26</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub>S: C, 67.21; H, 6.07; N, 6.03. Found: C, 66.65; H, 6.08; N, 5.96.

15

### Example 20

Preparation of [2-cyclohexyl-1-(4-(4-thiazolylmethoxy)phenyl)eth-1-yl]-2-iminoxypropionic acid

The title compound was prepared according to the procedure of Example 2, except substituting 2-cyclohexyl-1-(4-(4-thiazolylmethoxy)phenyl)ethan-1-ol, 20 prepared as described in Example 18, step 2, for cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methanol. m.p. 132-134 °C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 0.95 (m, 2H), 1.17 (m, 4H), 1.72 (m, 7H), 1.95 (s, 3H), 5.21 (m, 3H), 7.01 (d, J = 9 Hz, 2H), 7.25 (d, J = 9 Hz, 2H), 7.78 (d, J = 2 Hz, 1H), 9.13 (d, J = 2 Hz, 1H). MS (DCI/NH<sub>3</sub>) m/e 403 (M+H)<sup>+</sup>, 420 (M+H+NH<sub>3</sub>)<sup>+</sup>. Analysis 25 calcd. for C<sub>21</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>S: C, 62.65; H, 6.51; N, 6.96. Found: C, 62.62; H, 6.43; N, 6.89.

### Example 21

Preparation of [3-Cyclohexyl-2-[4-(2-quinolylmethoxy)phenyl]prop-1-yl]iminoxycetic acid

30 Step 1: 3-cyclohexyl-2-[4-(2-quinolylmethoxy)phenyl]propan-1-ol.

To a solution of 3-cyclohexyl-2-[4-(2-quinolylmethoxy)phenyl]propionic acid, prepared according to the procedure of K. Mohrs *et al.* United States patent number 4,970,215, (1.37 g, 3.5 mmol) in THF (40 mL) at -10 °C was added triethylamine (0.5 mL, 3.6 mmol) and then dropwise a solution of ethyl 35 chloroformate (0.36 mL, 3.6 mmol) in THF (10 mL). The reaction was stirred for 15 minutes at -10 to -5 °C and then was allowed to warm to 0 °C. To the mixture was

added sodium borohydride (380 mg, 10 mmol) followed by the dropwise addition of methanol (30 mL) for 30 minutes at 0 °C. The resulting mixture was stirred for an additional 20 minutes and then was neutralized with 10% citric acid and extracted with ethyl acetate (100 mL). The ethyl acetate extract was washed with water and brine,  
5 dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with 2:1 hexane-ethyl acetate to provide 1.14 g of 3-cyclohexyl-2-(4-(2-quinolylmethoxy)phenyl)propan-1-ol as an oil.

10 Step 2: *N*-phthaloyl-*O*-{1-(3-cyclohexyl-2-[4-(2-quinolylmethoxy)phenyl]})propyl}hydroxylamine.

To a solution of the 3-cyclohexyl-2-(4-(2-quinolylmethoxy)phenyl)propan-1-ol prepared in step 1, (1.10g, 3.00 mmol), triphenylphosphine (1.31 g, 5.00 mmol) and *N*-hydroxyphthalimide (490 mg, 3.00 mmol) in THF (95 mL) was added dropwise a solution of DEAD (0.83 mL; 5 mmol) in THF (5 mL). The resulting  
15 mixture was stirred at ambient temperature for 12 hours and then was concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with 35:1 methylene chloride-ethyl acetate to afford 1.5 g of *N*-phthaloyl-*O*-{1-(3-cyclohexyl-2-[4-(2-quinolylmethoxy)phenyl]})propyl}hydroxylamine.

20 Step 3: *O*-{1-(3-cyclohexyl-2-[4-(2-quinolylmethoxy)phenyl]})propyl}hydroxylamine.

A mixture of *N*-phthaloyl-*O*-{1-(3-cyclohexyl-2-[4-(2-quinolylmethoxy)phenyl]})propyl}hydroxylamine (1.4 g, 2.7 mmol), prepared as in step 2, and hydrazine hydrate (0.30 mL, 6.0 mmol) in 1:1 ethanol-methylene chloride (60 mL)  
25 was refluxed for 30 minutes and then cooled to ambient temperature. 10% Sodium carbonate (30 mL) was added and the mixture was extracted with ethyl acetate (100 mL). The organic extract was washed with water (2x50 mL) and brine, dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was purified on a silica gel column eluting with 3:1 methylene chloride-ethyl acetate to afford 1.0 g of *O*-{1-(3-cyclohexyl-2-[4-(2-quinolylmethoxy)phenyl]})propyl}hydroxylamine.  
30

Step 4: 1-{3-Cyclohexyl-2-[4-(2-quinolylmethoxy)phenyl]})propyl}iminoxyacetic acid.

A solution of *O*-{1-(3-cyclohexyl-2-[4-(2-quinolylmethoxy)phenyl]})propyl}hydroxylamine (390 mg, 1 mmol), prepared as in step 3, glyoxylic acid  
35 hydrate (100 mg, 1.00 mmol) and sodium acetate trihydrate (136 mg, 1.00 mmol) in

methanol (25 mL)-THF (10 mL)-water (5 mL) was stirred at ambient temperature for 16 hours. The organics were removed *in vacuo*, and to the residue was added water (10 mL) and 1N NaOH (2 mL). The resulting mixture was washed with ethyl ether (15 mL) and acidified with 10% citric acid. The precipitated solid was filtered and  
5 recrystallized from ethyl acetate-hexane to provide 320 mg of 1-{3-Cyclohexyl-2-[4-(2-quinolylmethoxy)phenyl]-propyl}iminoxyacetic acid. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 0.8 (m, 2H), 1.05 (m, 4H), 1.53 (m, 6H), 1.74 (m, 1H), 3.05 (quintet, J = 7 Hz, 1H), 4.2 (dd, J = 7, 2 Hz, 2H), 5.35 (s, 2H), 7.0 (d, J = 9 Hz, 2H), 7.18 (d, J = 9 Hz, 2H), 7.47 (s, 1H), 7.63 (t, J = 8 Hz, 1H), 7.7 (d, J = 8 Hz, 1H), 7.8 (m, 1H), 8.02 (t, J = 8 Hz, 2H), 8.42 (d, J = 8 Hz, 1H). MS (DCI/NH<sub>3</sub>)  
10 m/e 447 (M+H)<sup>+</sup>. Analysis calcd. for C<sub>27</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub>: C, 72.62; H, 6.77; N, 6.27. Found: C, 72.46; H, 6.72; N, 6.13.

### Example 22

15 Preparation of [3-cyclohexyl-2-(4-(2-quinolylmethoxy)phenyl)prop-1-yl]-2-iminoxypropionic acid

Step 1: 3-cyclohexyl-2-(4-(2-quinolylmethoxy)phenyl)prop-1-yl]-2-iminoxypropionic acid methyl ester.

A mixture of O-{1-(3-cyclohexyl-2-[4-(2-quinolylmethoxy)phenyl])propyl}hydroxylamine (320 mg, 0.80 mmol), prepared as  
20 in Example 21, step 3, methyl pyruvate (0.092 mL, 1.00 mmol) and acetic acid (0.06 mL) in 2:1 methanol-THF (30 mL) was stirred at ambient temperature for 20 hours and then was concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with 3:1 hexane-ethyl acetate to provide 260 mg of 3-cyclohexyl-2-(4-(2-quinolylmethoxy)phenyl)prop-1-yl]-2-iminoxypropionic acid methyl ester.  
25

Step 2: 3-cyclohexyl-2-(4-(2-quinolylmethoxy)phenyl)prop-1-yl]-2-iminoxypropionic acid.

The 3-cyclohexyl-2-(4-(2-quinolylmethoxy)phenyl)prop-1-yl]-2-iminoxypropionic acid methyl ester prepared in step 1 was hydrolyzed with 1N  
30 sodium hydroxide (2 mL) at 50 °C for 90 minutes. The methanol was removed *in vacuo*, and the aqueous solution was diluted with 20 mL of water. The resulting solution was acidified with 10% citric acid, washed with ethyl acetate, dried over magnesium sulfate and concentrated *in vacuo* to afford the title compound as an  
35 amorphous solid. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 0.8 (m, 2H), 1.05 (m, 4H), 1.53 (m, 6H), 1.72 (m, 1H), 1.82 (s, 3H), 3.05 (quintet, J = 7 Hz, 1H), 4.2 (m,

2H), 5.33 (s, 2H), 7.0 (d, J = 9 Hz, 2H), 7.17 (d, J = 9 Hz, 2H), 7.63 (t, J = 8 Hz, 1H), 7.7 (d, J = 8 Hz, 1H), 7.8 (m, 1H), 8.02 (t, J = 8 Hz, 2H), 8.42 (d, J = 8 Hz, 1H). MS (DCI/NH<sub>3</sub>) m/e 461 (M+H)<sup>+</sup>. IR (CDCl<sub>3</sub>): 3440, 1760, 1600 cm<sup>-1</sup>.

Analysis calcd. for C<sub>28</sub>H<sub>32</sub>N<sub>2</sub>O<sub>4</sub>: C, 73.02; H, 7.00; N, 6.08. Found: C, 72.26;

5 H, 6.89; N, 5.87.

### Example 23

#### Preparation of [3-Cyclohexyl-2-(4-(2-quinolylmethoxy)phenyl)prop-1-yl]-3-iminoxy-(2,2-dimethyl)propionic acid

10 The title compound was prepared according to the procedure of Example 22, except substituting 3-carbomethoxy-2,2-dimethylpropionaldehyde for methyl pyruvate. *E*-isomer: <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 0.82 (m, 2H), 1.05 (m, 4H), 1.12 (s, 6H), 1.52 (m, 6H), 1.7 (m, 1H), 2.97 (m, 1H), 3.92 (d, J = 7 Hz, 2H), 5.33 (s, 2H), 6.98 (d, J = 9 Hz, 2H), 7.14 (d, J = 9 Hz, 2H), 7.48 (s, 1H), 7.62  
15 (m, 1H), 7.68 (d, J = 8 Hz, 1H), 7.8 (m, 1H), 8.02 (t, J = 8 Hz, 2H), 8.42 (d, J = 8 Hz, 1H). MS (DCI/NH<sub>3</sub>) m/e 489 (M+H)<sup>+</sup>. *Z*-isomer: <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 0.83 (m, 2H), 1.03 (m, 4H), 1.22 (s, 6H), 1.55 (m, 6H), 1.7 (m, 1H), 3.0 (m, 1H), 3.97 (d, J = 7 Hz, 2H), 5.33 (s, 2H), 6.98 (d, J = 9 Hz, 2H), 7.14 (d, J = 9 Hz, 2H), 7.43 (s, 1H), 7.65 (m, 2H), 7.8 (m, 1H), 8.02 (t, J = 8 Hz, 2H),  
20 8.42 (d, J = 8 Hz, 1H). MS (DCI/NH<sub>3</sub>) m/e 489 (M+H)<sup>+</sup>.

### Example 24

#### Preparation of [4-(4-fluorophenyl)-1-(4-(2-quinolylmethoxy)phenyl)but-1-yl]iminoxyacetic acid

25 The title compound was prepared according to the procedure of Example 12, except substituting 1-bromo-4-(4-fluorophenyl)butane for 1-bromo-4-(4-chlorophenyl)butane. m.p. 152-154 °C <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.55 (m, 2H), 1.73 (m, 1H), 1.92 (m, 1H), 2.58 (t, J = 7 Hz, 2H), 5.18 (t, J = 7 Hz, 1H), 5.36 (s, 2H), 7.06 (m, 4H), 7.18 (m, 2H), 7.25 (d, J = 9 Hz, 2H), 7.57 (s,  
30 1H), 7.63 (m, 2H), 7.78 (m, 1H), 8.0 (t, J = 8 Hz, 2H), 8.43 (d, J = 8 Hz, 1H). MS (DCI/NH<sub>3</sub>) m/e 473 (M+H)<sup>+</sup>. Analysis calcd. for C<sub>28</sub>H<sub>25</sub>FN<sub>2</sub>O<sub>4</sub>: C, 71.11; H, 5.33; N, 6.03. Found: C, 71.24; H, 5.36; N, 5.86.

**Example 25**Preparation of [4-(4-fluorophenyl)-1-(4-(2-quinolylmethoxy)phenyl)but-1-yl]-2-iminoxypropionic acid.

The title compound was prepared according to the procedure of Example 12, except substituting 1-bromo-4-(4-fluorophenyl)butane for 1-bromo-4-(4-chlorophenyl)butane and substituting pyruvic acid for glyoxylic acid. m.p. 160-162 °C <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.55 (m, 2H), 1.73 (m, 2H), 1.97 (s, 3H), 2.57 (t, J = 7 Hz, 2H), 5.18 (t, J = 7 Hz, 1H), 5.35 (s, 2H), 7.05 (t, J = 9 Hz, 4H), 7.18 (m, 2H), 7.23 (d, J = 9 Hz, 2H), 7.63 (m, 1H), 7.68 (d, J = 8 Hz, 1H), 7.79 (m, 1H), 8.02 (t, J = 8 Hz, 2H), 8.42 (d, J = 8 Hz, 1H). MS (DCI/NH<sub>3</sub>) m/e 487 (M+H)<sup>+</sup>. Analysis calcd. for C<sub>29</sub>H<sub>27</sub>N<sub>2</sub>O<sub>4</sub>: C, 71.58; H, 5.59; N, 5.76. Found: C, 72.05; H, 5.57; N, 5.77.

**Example 26**Preparation of [2-cyclohexyl-2-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]-iminoxylacetic acid.

The title compound was prepared according to the procedure of Example 21, except substituting 2-cyclohexyl-2-(4-(2-quinolylmethoxy)phenyl)acetic acid for 3-cyclohexyl-2-(4-(2-quinolylmethoxy)phenyl)propionic acid. m.p. 68-70 °C (recrystallized from ethyl acetate-hexane). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 1.0 (m, 5H), 1.42 (m, 1H), 1.6 (m, 4H), 1.83 (m, 1H), 2.75 (m, 1H), 4.44 (m, 2H), 5.34 (s, 2H), 7.0 (d, J = 9 Hz, 2H), 7.12 (d, J = 9 Hz, 2H), 7.43 (s, 1H), 7.63 (m, 1H), 7.7 (d, J = 8 Hz, 1H), 7.8 (m, 1H), 8.0 (t, J = 8 Hz, 2H), 8.42 (d, J = 8 Hz, 1H). MS (DCI/NH<sub>3</sub>) m/e 433 (M+H)<sup>+</sup>. IR (in CDCl<sub>3</sub>): 1760, 1695, 1600 cm<sup>-1</sup>. Analysis calcd. for C<sub>26</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub>: C, 72.20; H, 6.53; N, 6.48. Found: C, 71.65; H, 6.63; N, 6.38.

**Example 27**Preparation of [2-Cycloheptyl-2-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]iminoxylacetic acid.

The title compound was prepared according to the procedure of Example 21, except substituting 2-cycloheptyl-2-(4-(2-quinolylmethoxy)phenyl)acetic acid for 3-cyclohexyl-2-(4-(2-quinolylmethoxy)phenyl)propionic acid. m.p. 73-74 °C (recrystallized from ethyl acetate-hexane). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 1.05 (m, 1H), 1.43 (m, 10H), 1.78 (m, 2H), 2.85 (q, J = 7 Hz, 1H), 4.44 (m, 2H), 5.33 (s, 2H), 7.0 (d, J = 9 Hz, 2H), 7.14 (d, J = 9 Hz, 2H), 7.43 (s, 1H), 7.52 (m, 1H), 7.68 (d, J = 8 Hz, 1H), 7.8 (m, 1H), 8.03 (t, J = 8 Hz, 2H), 8.42 (d, J = 8 Hz,



1H). MS (DCI/NH<sub>3</sub>) m/e 447 (M+H)<sup>+</sup>. IR (CDCl<sub>3</sub>): 1760, 1695, 1600 cm<sup>-1</sup>.  
Analysis calcd. for C<sub>27</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub>: C, 72.62; H, 6.77; N, 6.27. Found: C, 72.19;  
H, 6.75; N, 6.13.

#### Example 28

5 Preparation of [2-cycloheptyl-2-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]-3-iminoxy-2,2-dimethylpropionic acid.

The title compound was prepared according to the procedure of Example 21, except substituting 2-cycloheptyl-2-[4-(2-quinolylmethoxy)phenyl]acetic acid for 3-cyclohexyl-2-[4-(2-quinolylmethoxy)phenyl]propionic acid and substituting 3-carbomethoxy-2,2-dimethylpropionaldehyde for glyoxylic acid. m.p. 106-107 °C  
10 (recrystallized from ethyl acetate-hexane). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 1.03 (m, 1H), 1.22 (s + m, 8H), 1.38 (m, 3H), 1.5 m, 5H), 1.77 (m, 2H), 2.78 (m, 1H), 4.2 (m, 2H), 5.33 (s, 2H), 6.97 (d, J = 9 Hz, 2H), 7.12 (d, J = 9 Hz, 2H), 7.38 (s, 1H), 7.64 (m, 1H), 7.7 (d, J = 8 Hz, 1H), 7.8 (m, 1H), 8.02 (t, J = 8 Hz, 2H),  
15 8.43 (d, J = 8 Hz, 1H). MS (DCI/NH<sub>3</sub>) m/e 489 (M+H)<sup>+</sup>. Analysis calcd. for C<sub>30</sub>H<sub>36</sub>N<sub>2</sub>O<sub>4</sub>: C, 73.74; H, 7.43; N, 5.73. Found: C, 73.67; H, 7.46; N, 5.61.

#### Example 29

20 Preparation of [2-cyclopentyl-2-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]iminoxyacetic acid.

The title compound was prepared according to the procedure of Example 21, except substituting 2-cyclopentyl-2-[4-(2-quinolylmethoxy)phenyl]acetic acid for 3-cyclohexyl-2-[4-(2-quinolylmethoxy)phenyl]propionic acid. m.p. 88-90 °C  
(recrystallized from ethyl acetate-hexane). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 0.96  
25 (m, 1H), 1.35 (m, 6H), 1.85 (m, 1H), 2.03 (m, 1H), 2.72 (m, 1H), 4.4 (m, 2H), 5.35 (s, 2H), 7.0 (d, J = 9 Hz, 2H), 7.15 (d, J = 9 Hz, 2H), 7.43 (s, 1H), 7.63 (m, 1H), 7.7 (d, J = 8 Hz, 1H), 7.8 (m, 1H), 8.03 (t, J = 8 Hz, 2H), 8.43 (d, J = 8 Hz, 1H), 13.25 (broad s, 1H). MS (DCI/NH<sub>3</sub>) m/e 419 (M+H)<sup>+</sup>. Analysis calcd. for C<sub>25</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub> · 0.5 H<sub>2</sub>O: C, 70.24; H, 6.37; N, 6.55. Found: C, 70.47; H, 6.24;  
30 N, 6.39.

**Example 30**Preparation of [Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-Z-2-iminoxypionic acid methyl ester.

- The mixture of *Z* and *E* isomers obtained according to the procedure of Example 2 was separated by chromatography on silica gel (hexane-ethyl ether 3:1). Example 2 was separated by chromatography on silica gel (hexane-ethyl ether 3:1). [Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-Z-2-iminoxypionic acid methyl ester (140 mg). <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ: 0.93 (m, 3H), 1.08 (m, 2H), 1.32 (m, 1H), 1.60 (m, 4H), 1.68 (m, 1H), 1.91 (s, 3H), 3.80 (s, 3H), 4.73 (d, 1H, J = 7 Hz), 5.36 (s, 2H), 7.03 (d, 2H, J = 9 Hz), 7.14 (d, 2H, J = 9 Hz), 7.62 (m, 1H), 7.69 (d, 1H, J = 8 Hz), 7.78 (m, 1H), 8.02 (m, 2H), 8.43 (d, 1H, J = 8 Hz). MS (DCI/NH<sub>3</sub>) m/e 447 (M + H)<sup>+</sup>. Analysis calcd. for C<sub>27</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub>: C, 72.62; H, 6.77; N, 6.27. Found: C, 72.49; H, 6.61; N, 5.99.

**Example 31**

15 Preparation of [Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-E-2-iminoxypionic acid methyl ester.

- The desired compound (960 mg), was obtained in the chromatography described in Example 30. *E* isomer: m.p. 105-106°C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ: 1.05 (m, 5H), 1.33 (m, 1H), 1.67 (m, 4H), 1.85 (m, 1H), 2.03 (s, 3H), 3.68 (s, 3H), 4.95 (d, 1H, J = 7 Hz), 7.04 (9d, 2H, J = 9 Hz), 7.19 (d, 2H, J = 9 Hz), 7.63 (m, 1H), 7.67 (d, 1H, J = 8 Hz), 7.80 (m, 1H), 8.00 (m, 2H), 8.42 (d, 1H, J = 8 Hz). MS (DCI/NH<sub>3</sub>) m/e 447 (M + H)<sup>+</sup>. Analysis calcd. for C<sub>27</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub>: C, 72.62; H, 6.77; N, 6.27. Found: C, 72.45; H, 7.11; N, 6.09.

**Example 32**

25 Preparation of [cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-Z-2-iminoxypionic acid.

- To a solution of [Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-Z-2-iminoxypionic acid methyl ester (74 mg, 0.17 mmol), prepared as in Example 30, in dioxane-methanol (2:1) (12 ml) was added 1N sodium hydroxide (1 ml) and the resulting mixture was stirred at room temperature for 24 hours. The organics were then removed *in vacuo*, and the residue was diluted with water (10 ml) and acidified to pH 3. The precipitated product was filtered, dried *in vacuo* and recrystallized from ethyl acetate-hexane to provide [Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-Z-2-iminoxypionic acid. m.p. 142-144 °C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.07 (m, 5H), 1.30 (m, 1H), 1.62 (m, 5H), 1.87 (s, 3H), 4.70 (d, 1H, J = 7 Hz),

5.35 (s, 2H), 7.02 (d, 2H, J = 9 Hz), 7.14 (d, 2H, J = 9 Hz), 7.62 (m, 1H), 7.68 (d, 1H, J = 9 Hz), 7.80 (m, 1H), 8.01 (m, 2H), 8.41 (d, 1H, J = 9 Hz), 13.56 (broad s, 1H). MS (DCI/NH<sub>3</sub>) m/e 433 (M + H)<sup>+</sup>. Analysis calcd. for C<sub>26</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub>: C, 72.20; H, 6.53; N, 6.48. Found: C, 71.71; H, 6.75; N, 6.16.

5

### Example 33

#### Preparation of [cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-E-2-iminoxypropionic acid.

The desired compound was prepared according to the method of Example 32, except substituting [Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-E-2-iminoxypropionic acid methyl ester (770 mg, 1.7 mmol), prepared as in Example 31, for [Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-Z-2-iminoxypropionic acid methyl ester. m.p. 183-184°C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.12 (m, 5H), 1.35 (m, 1H), 1.67 (m, 4H), 1.86 (m, 1H), 1.98 (s, 3H), 4.92 (d, 1H, J = 7 Hz), 5.35 (s, 2H), 7.03 (d, 2H, J = 9 Hz), 7.17 (d, 2H, J = 9 Hz), 7.62 (m, 1H), 7.68 (d, 1H, J = 9 Hz), 7.78 (m, 1H), 8.00 (m, 2H), 8.42 (d, 1H, J = 9 Hz). MS (DCI/NH<sub>3</sub>) m/e: 433 (M + H)<sup>+</sup>. Analysis calcd. for C<sub>26</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub>: C, 72.20; H, 6.53; N, 6.48. Found: C, 71.90; H, 6.75; N, 6.28.

20

### Example 34

#### Preparation of (R)-[Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-E-2-iminoxypropionic acid methyl ester.

##### Step 1: N-benzyloxy-(2R,3R)dibenzoyltartimide.

To a solution of dibenzoyl anhydride of tartaric acid (14.0 g, 40 mmol) in THF (100 ml) was added O-benzylhydroxylamine (5.4 g, 44 mmol) and the mixture was stirred at room temperature for 12 hours. The THF was then removed *in vacuo*, and the residue was redissolved in chloroform (100 ml). To the resulting solution at 0 °C was added dropwise thionyl chloride (3.65 ml, 50 mmol) and the mixture was allowed to warm to room temperature for 4 hours. The solution was then concentrated *in vacuo* and the residue was chromatographed (silica gel, methylene chloride-ethyl acetate 19:1) to afford 18.9 g of N-benzyloxy-(2R,3R)dibenzoyltartimide.

35

Step 2: *N*-hydroxy-(2*R*,3*R*)dibenzoyltartramide.

The *N*-benzyloxy-(2*R*,3*R*)dibenzoyltartramide prepared in step 1 was hydrogenated with hydrogen in ethyl acetate (250 ml) over 10% palladium on charcoal (1.9 g) under atmospheric pressure to provide, after filtration of the catalyst and  
5 evaporation of the solvent, 14 g of *N*-hydroxy-(2*R*,3*R*)dibenzoyltartramide,  $\alpha_D = +161.2$  ( $c = 0.5$ , THF).

Step 3: *N*-(*R*)-[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methoxy](2*R*,3*R*)dibenzoyltartramide.

10 To a solution of *N*-hydroxy-(2*R*,3*R*)dibenzoyltartramide (1.42 g, 4 mmol), prepared as in step 2, cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methanol (1.4 g, 4 mmol), prepared according to the procedure of Example 1, step 2, and triphenylphosphine (1.57 g, 6 mmol) in THF (50 ml) was added dropwise a solution of DEAD (0.96 ml, 6 mmol) in THF (5 ml), and the resulting mixture was stirred at  
15 room temperature for 4 hours. The mixture was then concentrated *in vacuo* and the residue was chromatographed twice. First using toluene-ethyl acetate, 19:1 to separate product from the triphenylphosphine oxide and diethyl hydrazine dicarboxylate and then hexane-methylene chloride-ethyl acetate (54:40:6) to separate diastereoisomers. The *N*-(*R*)-[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methoxy]-  
20 (2*R*,3*R*)dibenzoyltartramide (470 mg) was eluted first and the *N*-(*S*)-[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methoxy]-(2*R*,3*R*)-dibenzoyltartramide (310 mg) was eluted second.

Step 4: *O*-(*R*)-[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]hydroxylamine.

25 A mixture of *N*-(*R*)-[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methoxy]-(2*R*,3*R*)-dibenzoyltartramide (470 mg, 0.687 mmol), prepared as in step 3, and hydrazine hydrate (0.35 ml) in 1:1 ethanol-dioxane (30 ml) was refluxed for 30 min and then was allowed to cool to room temperature. To the mixture was added 10% sodium carbonate and the product was extracted with ethyl acetate (100 ml). The  
30 extract was washed with water, and brine, dried over  $\text{MgSO}_4$ , and concentrated *in vacuo*. The residue was purified on silica gel column (hexane-ethyl acetate 2:1) to provide 200 mg of *O*-(*R*)-[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]hydroxylamine.

35 Step 5: (*R*)-[Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*E*-2-iminoxypropionic acid methyl ester.

To a solution of the *O*-(*R*)-[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]hydroxylamine prepared in step 4 in dioxane (15 ml) and methanol (10 ml) were added acetic acid (0.03 ml), water (1 ml) and methyl pyruvate (0.06 ml, 0.6 mmol) and the reaction mixture was stirred at room temperature for 12 hours. The organics were removed *in vacuo* and the residue was extracted with ethyl acetate, dried over  $\text{MgSO}_4$ , and concentrated *in vacuo*. The residue was chromatographed (silica gel, hexane-ethyl ether 3:1) to provide 100 mg of (*R*)-[Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*E*-2-iminoxypropionic acid methyl ester,  $\alpha_D = -35.0$  ( $c = 0.1$ ,  $\text{CHCl}_3$ ). m.p. 99-101 °C.  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  1.60 (m, 5H), 1.35 (m, 1H), 1.64 (m, 4H), 1.77 (m, 1H), 2.03 (s, 3H), 3.67 (s, 3H), 4.95 (d, 1H,  $J = 7$  Hz), 5.36 (s, 2H), 7.03 (d, 2H,  $J = 9$  Hz), 7.18 (d, 2H,  $J = 9$  Hz), 7.65 (m, 2H), 7.79 (m, 1H), 8.01 (t, 2H,  $J = 9$  Hz), 8.41 (d, 1H,  $J = 9$  Hz). MS (DCI/ $\text{NH}_3$ )  $m/e$  447 ( $M + H$ ) $^+$ .

15

**Example 35****Preparation of (*R*)-[Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*E*-2-iminoxypropionic acid.**

To a solution of (*R*)-[Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*E*-2-iminoxypropionic acid methyl ester (80 mg, 0.18 mmol), prepared as in Example 34, in dioxane (6 ml) and methanol (3 ml) was added 1*N* NaOH (0.2 ml) and the resulting mixture was stirred at room temperature for 10 hours. The mixture was then concentrated *in vacuo*, the residue was diluted with water (5 ml) and acidified to pH 3. The solid was filtered, dried *in vacuo* and crystallized from ethyl acetate-hexane to afford 50 mg of (*R*)-[Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*E*-2-iminoxypropionic acid. m.p. 179-180 °C.  $\alpha_D = -18.0$  ( $c = 0.1$ ,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  1.11 (m, 5H), 1.37 (m, 1H), 1.65 (m, 4H), 1.87 (m, 1H), 2.00 (s, 3H), 4.42 (d, 1H,  $J = 7$  Hz), 5.36 (s, 2H), 7.03 (d, 2H,  $J = 9$  Hz), 7.19 (d, 2H,  $J = 9$  Hz), 7.65 (m, 2H), 7.78 (m, 1H), 8.01 (t, 2H,  $J = 9$  Hz), 8.41 (d, 1H,  $J = 9$  Hz), 12.89 (broad s, 1H). MS (DCI/ $\text{NH}_3$ )  $m/e$  433 ( $M + H$ ) $^+$ . Analysis calcd. for  $\text{C}_{26}\text{H}_{28}\text{N}_2\text{O}_4$ : C, 72.20; H, 6.53; N, 6.48. Found: C, 71.98; H, 6.44; N, 6.30.

**Example 36**

Preparation of (S)-[Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-E-2-iminoxypropionic acid methyl ester.

Step 1: N-(S)-[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methoxy]-(2S,3S)-dibenzoyltartramide.

To a solution of O-(RS)-[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)-methyl]hydroxylamine (253 mg, 1.50 mmol), prepared according to the procedure of Example 1, step 3, in THF (30 ml) was added (2S,3S)-dibenzoyltartaric acid anhydride (510 mg, 1.50 mmol), followed after 30 min by N-hydroxysuccinimide (230 mg, 2 mmol) and dicyclohexylcarbodiimide (412 mg, 2.00 mmol). The resulting mixture was stirred at room temperature for 14 hours. The mixture was then concentrated *in vacuo* and the residue was chromatographed (silica gel, hexane-methylene chloride-ethyl acetate (54:40:6) to afford 140 mg of N-(S)-[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methoxy]-(2S,3S)-dibenzoyltartramide (elutes first) and 70 mg of N-(R)-[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methoxy]-(2S,3S)-dibenzoyltartramide (elutes second).

Step 2: (S)-[Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-E-2-iminoxypropionic acid methyl ester.

The desired material was prepared as described in the procedure of Example 34, except substituting N-(S)-[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methoxy]-(2R,3R) dibenzoyltartramide, prepared as in step 1, for N-(R)-[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methoxy]-(2R,3R)-dibenzoyltartramide.  $\alpha_D = +33.3$  (c = 0.15, CHCl<sub>3</sub>). m.p. 96-98 °C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.11 (m, 5H), 1.35 (m, 1H), 1.64 (m, 4H), 1.87 (m, 1H), 2.03 (s, 3H), 3.68 (s, 3H), 4.94 (d, 1H, J = 7 Hz), 5.35 (s, 2H), 7.03 (d, 2H, J = 9 Hz), 7.18 (d, 2H, J = 9 Hz), 7.62 (m, 1H), 7.68 (d, 1H, J = 9 Hz), 7.79 (m, 1H), 8.01 (t, 2H, J = 9 Hz), 8.42 (d, 1H, J = 9 Hz). MS (DCI/NH<sub>3</sub>) m/e 447 (M + H)<sup>+</sup>.

**Example 37**

Preparation of (S)-[Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-E-2-iminoxypropionic acid.

The desired material was prepared according to the method of Example 35, except substituting (S)-[Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-E-2-iminoxypropionic acid methyl ester, prepared as in Example 36, for (R)-[Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-E-2-iminoxypropionic acid methyl ester.  $\alpha_D =$

16.7 ( $c = 0.15$ ,  $\text{CHCl}_3$ ); mp. 179-180°C;  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-d}_6$ )  $\delta$ : 1.12 (m, 5H), 1.36 (m, 1H), 1.67 (m, 4H), 1.85 (m, 1H), 2.00 (s, 3H), 4.92 (d, 1H,  $J = 7$  Hz), 5.35 (s, 2H), 7.03 (d, 2H,  $J = 9$  Hz), 7.18 (d, 2H,  $J = 9$  Hz), 7.65 (m, 2H), 7.80 (m, 1H), 8.00 (t, 2H,  $J = 9$  Hz), 8.42 (d, 1H,  $J = 9$  Hz), 12.88 (broad s, 1H);  
5 MS (DCI/ $\text{NH}_3$ )  $m/e$ : 433 ( $M + 1$ ); Analysis calcd. for  $\text{C}_{26}\text{H}_{28}\text{N}_2\text{O}_4$ : C, 72.20; H, 6.53; N, 6.48; Found: C, 72.01; H, 6.49; N, 6.27.

### Example 38

10 Preparation of [Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-Z-iminoxyacetic acid methyl ester.

A mixture of O-[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]hydroxylamine (347 mg, 1 mmol), prepared according to the procedure of Example 1, step 4, glyoxylic acid hydrate (92 mg, 1.0 mmol) and acetic acid (0.06 ml, 1.0 mmol) in dioxane (15 ml), water (1 ml) and  
15 methanol (10 ml) was stirred at ambient temperature for 8 hours. The organics were removed *in vacuo* and the product was extracted with ethyl acetate. The extract was dried over  $\text{MgSO}_4$ , and concentrated *in vacuo*. The residue was dissolved in DMF (25 ml) and was treated with sodium bicarbonate (84 mg, 1.0 mmol) and iodomethane (3 ml), and the resulting mixture was stirred at ambient temperature for 72 hours. The  
20 reaction mixture was then poured into water (50 ml), and extracted with ethyl acetate. The organic extract was washed with water and brine, dried over anhydrous  $\text{MgSO}_4$  and concentrated *in vacuo*. The residue was chromatographed (silica gel, hexane-ethyl ether 25:10) to afford 18 mg of [Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-Z-iminoxy acetic acid methyl ester.  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-d}_6$ )  $\delta$  1.10 (m,  
25 5H), 1.33 (m, 1H), 1.56 (m, 4H), 1.85 (m, 1H), 3.75 (s, 3H), 4.84 (d, 1H,  $J = 7$  Hz), 5.36 (s, 2H), 7.03 (d, 2H,  $J = 9$  Hz), 7.15 (d, 2H,  $J = 9$  Hz), 7.26 (s, 1H), 7.62 (m, 1H), 7.78 (d, 1H,  $J = 9$  Hz), 7.79 (m, 1H), 8.01 (t, 2H,  $J = 9$  Hz), 8.42 (d, 1H,  $J = 9$  Hz). MS (DCI/ $\text{NH}_3$ )  $m/e$  433 ( $M + H$ ) $^+$ .

30

### Example 39

Preparation of [Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-E-iminoxyacetic acid methyl ester.

[Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-E-iminoxy acetic acid methyl ester (225 mg), was isolated from the chromatography described in Example  
35 38.  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-d}_6$ )  $\delta$  1.10 (m, 5H), 1.28 (m, 1H), 1.65 (m, 4H), 1.90 (m, 1H), 3.69 (s, 3H), 4.42 (d, 1H,  $J = 7$  Hz), 5.36 (s, 2H), 7.05 (d, 2H,  $J =$

9 Hz), 7.20 (d, 2H,  $J = 9$  Hz), 7.62 (m, 1H), 7.78 (m, 2H), 7.80 (m, 1H), 8.01 (m, 2H), 8.42 (d, 1H,  $J = 9$  Hz). MS (DCI/NH<sub>3</sub>)  $m/e$  433 ( $M + H$ )<sup>+</sup>.

#### Example 40

5 Preparation of [Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-E-iminoxycetic acid.

The desired material was prepared according to the method of Example 35, except substituting [Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-E-iminoxycetic acid methyl ester, prepared as in Example 39, for (R)-[Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-E-2-iminoxypionic acid methyl ester. m.p. 197-198 °C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.10 (m, 5H), 1.68 (m, 1H), 1.65 (m, 4H), 1.90 (m, 1H), 4.89 (d, 1H,  $J = 7$  Hz), 5.35 (s, 2H), 7.04 (d, 2H,  $J = 9$  Hz), 7.18 (d, 2H,  $J = 9$  Hz), 7.56 (s, 1H), 7.62 (m, 1H), 7.78 (d, 1H,  $J = 9$  Hz), 7.80 (m, 1H), 8.00 (t, 2H,  $J = 9$  Hz), 8.41 (d, 1H,  $J = 9$  Hz), 13.16 (broad s, 1H). MS (DCI/NH<sub>3</sub>)  $m/e$ : 419 ( $M + H$ )<sup>+</sup>. Analysis calcd. for C<sub>25</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>: C, 71.75; H, 6.26; N, 6.69. Found: C, 71.69; H, 6.50; N, 6.63.

#### Example 41

20 Preparation of [2-phenyl-1-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]-Z-2-iminoxypionic acid.

The desired material was prepared according to the method of Example 2, except substituting benzylmagnesium chloride for cyclohexylmagnesium chloride and separating the mixture of isomers by chromatography as described in Example 38. m.p. 107-108 °C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.88 (s, 3H), 2.94 (dd, 1H,  $J = 15$  and 7 Hz), 3.10 (dd, 1H,  $J = 15$  and 7 Hz), 5.19 (t, 1H,  $J = 7$  Hz), 5.34 (s, 2H), 7.00 (d, 2H,  $J = 9$  Hz), 7.15 (m, 7H), 7.62 (m, 1H), 7.68 (d, 1H,  $J = 9$  Hz), 8.00 (t, 2H,  $J = 9$  Hz), 8.42 (d, 1H,  $J = 9$  Hz). MS (DCI/NH<sub>3</sub>)  $m/e$  441 ( $M + H$ )<sup>+</sup>. Analysis calcd. for C<sub>27</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>·H<sub>2</sub>O: C, 70.73; H, 5.72; N, 6.11. Found: C, 70.05; H, 5.49; N, 6.36.

#### Example 42

30 Preparation of [2-phenyl-1-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]-E-2-iminoxypionic acid.

The desired compound was obtained from the reaction and chromatography described in Example 41. mp. 186-187 °C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.94 (s, 3H), 3.07 (dd, 1H,  $J = 15$  and 7 Hz), 3.22 (dd, 1H,  $J = 15$  and 7 Hz), 5.35 (s+m, 3H), 7.02 (d, 2H,  $J = 9$  Hz), 7.21 (m, 7H), 7.62 (m, 1H), 7.68 (d, 1H,  $J = 9$



Hz), 7.98 (m, 1H), 8.00 (t, 2H,  $J = 9$  Hz), 8.42 (d, 1H,  $J = 9$  Hz). MS (DCI/ $\text{NH}_3$ )  $m/e$  441 ( $M + H$ )<sup>+</sup>. Analysis calcd. for  $\text{C}_{27}\text{H}_{24}\text{N}_2\text{O}_4 \times 0.5 \text{ H}_2\text{O}$ : C, 72.15; H, 5.61; N, 6.23. Found: C, 72.58; H, 5.87; N, 6.01.

5

**Example 43**

Preparation of [2-thienyl-(4-(2-quinolylmethoxy)phenyl)methyl]-E-2-iminoxypropionic acid.

The desired material was prepared according to the procedure of Example 2, except substituting 2-thienyllithium for cyclohexylmagnesium chloride. m.p. 72-74  
10 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-d}_6$ )  $\delta$  2.03 (s, 3H), 5.38 (s, 2H), 6.57 (s, 1H), 6.98 (m, 2H), 7.10 (m, 2H), 7.36 (m, 2H), 7.51 (m, 1H), 7.63 (m, 1H), 7.69 (d, 1H,  $J = 9$  Hz), 7.80 (m, 1H), 8.00 (t, 2H,  $J = 9$  Hz), 8.42 (d, 1H,  $J = 9$  Hz). MS (DCI/ $\text{NH}_3$ )  $m/e$  433 ( $M + H$ )<sup>+</sup>. Analysis calcd. for  $\text{C}_{24}\text{H}_{20}\text{N}_2\text{O}_4\text{S}$ : C, 66.65; H, 4.66; N, 6.48. Found: C, 65.96; H, 4.44; N, 6.11.

15

**Example 44**

Preparation of [Cyclohexyl-(2-chloro-4-(2-quinolylmethoxy)phenyl)methyl]-E-2-iminoxypropionic acid.

The desired material was prepared according to the procedure of Example 2, except substituting 2-chloro-4-(2-quinolylmethoxy)benzaldehyde for 4-(2-  
20 quinolylmethoxy) benzaldehyde. m.p. 153-155 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-d}_6$ )  $\delta$  1.14 (m, 5H), 1.41 (m, 1H), 1.65 (m, 3H), 1.80 (m, 2H), 2.00 (s, 3H), 5.30 (d, 1H,  $J = 7$  Hz), 5.39 (s, 2H), 7.07 (dd, 1H,  $J = 9$  and 3 Hz), 7.18 (d, 1H,  $J = 3$  Hz), 7.23 (d, 1H,  $J = 9$  Hz), 7.65 (m, 2H), 7.80 (m, 1H), 8.02 (t, 2H,  $J = 9$  Hz),  
25 8.43 (d, 1H,  $J = 9$  Hz). MS (DCI/ $\text{NH}_3$ )  $m/e$  467 ( $M + H$ )<sup>+</sup>. Analysis calcd. for  $\text{C}_{26}\text{H}_{27}\text{ClN}_2\text{O}_4$ : C, 66.88; H, 5.83; N, 6.00. Found: C, 66.89; H, 5.89; N, 5.82.

**Example 45**

Preparation of [Cyclohexyl-(3-chloro-4-(2-quinolylmethoxy)phenyl)methyl]-E-2-iminoxypropionic acid.

The desired material was prepared according to the procedure of Example 2, except substituting 3-chloro-4-(2-quinolylmethoxy)benzaldehyde for 4-(2-  
30 quinolylmethoxy) benzaldehyde. m.p. 90-92 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-d}_6$ )  $\delta$  1.10 (m, 5H), 1.36 (m, 1H), 1.70 (m, 5H), 2.00 (s, 3H), 4.94 (d, 1H,  $J = 7$  Hz), 5.46 (s, 2H), 7.18 (dd, 1H,  $J = 7$  and 2 Hz), 7.23 (d, 1H,  $J = 7$  Hz), 7.35 (d, 1H,  $J = 2$  Hz), 7.62 (m, 1H), 7.72 (d, 1H,  $J = 9$  Hz), 7.80 (m, 1H), 8.02 (t, 2H,  $J = 9$

Hz), 8.45 (d, 1H, J = 9 Hz). MS (DCI/NH<sub>3</sub>) m/e 467 (M + H)<sup>+</sup>. Analysis calcd. for C<sub>26</sub>H<sub>27</sub>ClN<sub>2</sub>O<sub>4</sub>: C, 66.88; H, 5.83; N, 6.00. Found: C, 67.03; H, 5.87; N, 5.82.

#### Example 46

5 Preparation of [Cyclohexyl-(2-chloro-4-(2-quinolylmethoxy)phenyl)methyl]-Z-2-iminoxypropionic acid.

The desired material was prepared according to the procedure of Example 2, except substituting 3-chloro-4-(2-quinolylmethoxy)benzaldehyde for 4-(2-quinolylmethoxy) benzaldehyde. m.p. 182-183 °C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.04 (m, 5H), 1.33 (m, 1H), 1.60 (m, 4H), 1.82 (m, 1H), 1.88 (s, 3H), 4.74  
10 (d, 1H, J = 7 Hz), 5.46 (s, 2H), 7.13 (dd, 1H, J = 7 and 2 Hz), 7.23 (d, 1H, J = 7 Hz), 7.30 (d, 1H, J = 2 Hz), 7.63 (m, 1H), 7.72 (d, 1H, J = 9 Hz), 7.80 (m, 1H), 8.01 (t, 2H, J = 9 Hz), 8.45 (d, 1H, J = 9 Hz). MS (DCI/NH<sub>3</sub>) m/e 467 (M + H)<sup>+</sup>.

#### Example 47

15 Preparation of [3-methyl-3-phenyl-1-[4-(2-quinolylmethoxy)phenyl]but-1-yl]-Z-2-iminoxypropionic acid.

The desired material was prepared according to the procedure of Example 2, except substituting 2-methyl-2-phenyl-1-propylmagnesium chloride for  
20 cyclohexylmagnesium chloride. m.p. 112-113 °C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.21 (s, 3H), 1.36 (s, 3H), 1.83 (9s, 3H), 2.00 (m, 2H), 4.65 (dd, 1H, J = 7 and 3 Hz), 5.33 (s, 2H), 6.98 (m, 4H), 7.19 (m, 1H), 7.31 (m, 4H), 7.65 (m, 2H), 7.80 (m, 1H), 8.00 (t, 2H, J = 9 Hz), 8.41 (d, 1H, J = 9 Hz). MS (DCI/NH<sub>3</sub>) m/e 483 (M + H)<sup>+</sup>. Analysis calcd. for C<sub>30</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub>·1.5 H<sub>2</sub>O: C, 70.71; H, 6.53; N, 5.50.  
25 Found: 70.72; H, 5.97; N, 5.39.

#### Example 48

Preparation of [3-methyl-3-phenyl-1-[4-(2-quinolylmethoxy)phenyl]but-1-yl]-E-2-iminoxypropionic acid.

30 The desired material was prepared according to the procedure of Example 2, except substituting 2-methyl-2-phenyl-1-propylmagnesium chloride for cyclohexylmagnesium chloride. m.p. 137-138 °C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.30 (s, 3H), 1.34 (s, 3H), 1.73 (s, 3H), 2.00 (dd, 1H, J = 15 and 3 Hz), 2.35 (dd, 1H, J = 15 and 9 Hz), 4.96 (dd, 1H, J = 9 and 3 Hz), 5.33 (s, 2H), 6.98 (d,  
35 2H, J = 9 Hz), 7.06 (d, 2H, J = 9 Hz), 7.15 (m, 1H), 7.30 (m, 2H), 7.37 (m, 2H), 7.64 (m, 2H), 7.79 (m, 1H), 8.00 (t, 2H, J = 9 Hz), 8.41 (d, 1H, J = 9 Hz), 12.80

(broad s, 1H). MS (DCI/NH<sub>3</sub>) m/e 483 (M + H)<sup>+</sup>. Analysis calcd for C<sub>30</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub>: C, 74.67; H, 6.27; N, 5.80. Found: C, 74.07; H, 6.38; N, 5.64.

#### Example 49

5 Preparation of [3-methyl-3-phenyl-1-(4-(2-quinolylmethoxy)phenyl)but-1-yl]-E-2-iminoxyacetic acid.

The desired material was prepared according to the procedure of Example 1, except substituting 2-methyl-2-phenyl-1-propylmagnesium chloride for cyclohexylmagnesium chloride. m.p. 73-75 °C. <sup>1</sup>H NMR (300 Mhz, DMSO-d<sub>6</sub>) δ  
10 1.25 (s, 3H), 1.34 (s, 3H), 2.05 (dd, 1H, J = 15 and 3 Hz), 2.30 (dd, 1H, J = 15 and 9 Hz), 4.87 (dd, 1H, J = 9 and 3 Hz), 5.33 (s, 2H), 6.98 (d, 2H, J = 9 Hz), 7.07 (d, 2H, J = 9 Hz), 7.16 (m, 1H), 7.31 (m, 5H), 7.64 (m, 2H), 7.80 (m, 1H), 8.00 (t, 2H, J = 9 Hz), 8.40 (d, 1H, J = 9 Hz), 13.13 (broad s, 1H). MS (DCI/NH<sub>3</sub>) m/e 469 (M + H)<sup>+</sup>. Analysis calcd. for C<sub>29</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub>: C, 74.34; H, 6.02; N, 5.98. Found: C, 74.09; H, 6.32; N, 5.84.

#### Example 50

20 Preparation of [4-(2-quinolylmethoxy)phenylpent-1-yl]-E-2-iminoxypropionic acid.

The desired material was prepared according to the procedure of Example 2, except substituting n-butylmagnesium chloride for cyclohexylmagnesium chloride. m.p. 118-119 °C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 0.85 (t, 3H, J = 7 Hz), 1.25 (m, 4H), 1.73 (m, 1H), 1.90 (m, 1H), 1.96 (s, 3H), 5.13 (t, 1H, J = 7 Hz), 5.36 (s, 2H), 7.04 (d, 2H, J = 9 Hz), 7.25 (d, 2H, J = 9 Hz), 7.62 (m, 1H), 7.68 (d, 1H, J = 9 Hz), 7.79 (m, 1H), 8.00 (t, 2H, J = 9 Hz), 8.42 (d, 1H, J = 9 Hz). MS  
25 (DCI/NH<sub>3</sub>) m/e 407 (M + H)<sup>+</sup>. Analysis calcd. for C<sub>24</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>: C, 70.92; H, 6.45; N, 6.89; Found. C, 70.52; H, 6.73; N, 6.78.

#### Example 51

30 Preparation of [4-(2-quinolylmethoxy)phenylpent-1-yl]-E-iminoxyacetic acid.

The desired material was prepared according to the procedure of Example 1, except substituting n-butylmagnesium chloride for cyclohexylmagnesium chloride. m.p. 124-126 °C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 0.83 (t, 3H, J = 7 Hz), 1.25 (m, 4H), 1.73 (m, 1H), 1.92 (m, 1H), 5.12 (t, 1H, J = 7 Hz), 5.36 (s, 2H), 7.06 (d, 2H, J = 9 Hz), 7.27 (d, 2H, J = 9 Hz), 7.55 (s, 1H), 7.62 (m, 1H), 7.68 (d, 1H, J = 9 Hz), 7.78 (m, 1H), 8.01 (m, 2H), 8.42 (d, 1H, J = 9 Hz). MS (DCI/NH<sub>3</sub>) m/e  
35 393 (M + H)<sup>+</sup>.

**Example 52**Preparation of [4-(2-quinolylmethoxy)phenyl]-but-3-en-1-yl]-E-iminoxy-2-propionic acid.

5 The desired material was prepared according to the procedure of Example 2, except substituting allylmagnesium chloride for cyclohexylmagnesium chloride. m.p. 123-124 °C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.97 (s, 3H), 2.57 (m, 1H), 2.60 (quintet, 1H, J = 7 Hz), 5.03 (m, 2H), 5.22 (t, 1H, J = 7 Hz), 5.36 (s, 2H), 5.70 (m, 1H), 7.05 (d, 2H, J = 9 Hz), 7.27 (d, 2H, J = 9 Hz), 7.62 (m, 1H), 7.68 (d, 10 1H, J = 9 Hz), 7.80 (m, 1H), 8.00 (t, 2H, J = 9 Hz), 8.42 (d, 1H, J = 9 Hz). MS (DCI/NH<sub>3</sub>) m/e 391 (M + H)<sup>+</sup>. Analysis calcd. for C<sub>23</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub>: C, 70.75; H, 5.68; N, 7.17; Found. H, 70.36; H, 5.92; N, 7.01.

**Example 53**

15 Preparation of [Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-E-2-iminoxy butanoic acid.

The desired material was prepared according to the procedure of Example 1, except substituting 2-ketobutyric acid for glyoxylic acid. m.p. 105 °C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ: 0.95 (m, 9H), 1.70 (m, 5H), 2.22 and 2.53 (two m, 1:2, 20 2H), 4.72 and 4.90 (two d, 1:2, 1H, J = 9 Hz), 5.35 (s, 2H), 7.05 (m, 2H), 7.15 (m, 2H), 7.65 (m, 2H), 7.80 (m, 1H), 8.02 (t, 2H, J = 9 Hz), 8.43 (d, 1H, J = 9 Hz). MS (DCI/NH<sub>3</sub>) m/e 447 (M + H)<sup>+</sup>. Analysis calcd. for C<sub>27</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub>·H<sub>2</sub>O: C, 69.81; H, 6.88; N, 6.03. Found: C, 70.00; H, 6.56; N, 5.50.

**Example 54**

25 Preparation of [Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-E-3-iminoxybutanoic acid.

The desired material was prepared according to the procedure of Example 2, except substituting 3-ketobutyric acid ethyl ester for pyruvic acid methyl ester. m.p. 85 °C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.10 (m, 6H), 1.73 (m, 8H), 2.54 (m, 30 2H), 4.65 (d, 1H, J = 9 Hz), 5.35 (s, 2H), 7.01 (m, 2H), 7.13 (m, 2H), 7.63 (m, 1H), 7.67 (d, 1H, J = 9 Hz), 7.80 (m, 1H), 8.02 (t, 2H, J = 9 Hz), 8.43 (d, 1H, J = 9 Hz). MS (DCI/NH<sub>3</sub>) m/e 447 (M + H)<sup>+</sup>. Analysis calcd. for C<sub>27</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub>·0.5H<sub>2</sub>O: C, 71.26; H, 6.86; N, 6.15. Found: C, 71.51; H, 7.15; N, 35 5.87.

**Example 55**

Preparation of [Cyclohexyl-1-(4-(2-quinolylmethoxy)phenyl)eth-2-yl]-2-iminoxy propionic acid.

Step 1: O-{1-(2-cyclohexyl-2-[4-(2-quinolylmethoxy)phenyl])ethyl}hydroxylamine.

5       The desired compound was prepared according to the method of Example 21, except substituting 2-cyclohexyl-2-(4-(2-quinolylmethoxy)phenyl)acetic acid for 3-cyclohexyl-2-(4-(2-quinolylmethoxy)phenyl)propionic acid.

10       Step 2: [Cyclohexyl-1-(4-(2-quinolylmethoxy)phenyl)eth-2-yl]-2-iminoxy propionic acid.

      The desired material was prepared according to the procedure of Example 22, except substituting O-{1-(2-cyclohexyl-2-[4-(2-quinolylmethoxy)phenyl])ethyl}hydroxylamine for O-{1-(3-cyclohexyl-2-[4-(2-quinolylmethoxy)phenyl])propyl}hydroxylamine. mp. 117-118°C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 0.76 (m, 1H), 1.03 (m, 4H), 1.41 (m, 1H), 1.62 (m, 4H), 1.75 (s, 3H), 1.83 (m, 1H), 2.74 (q, 1H, J = 6 Hz), 4.35 (dd, 1H, J = 10 and 6 Hz), 4.48 (dd, 1H, J = 10 and 6 Hz), 5.33 (s, 2H), 6.98 (d, 2H, J = 9 Hz), 7.12 (d, 2H, J = 9 Hz), 7.62 (m, 1H), 7.68 (d, 1H, J = 9 Hz), 7.80 (m, 1H), 8.00 (t, 2H, J = 9 Hz), 8.41 (d, 1H, J = 9 Hz). MS (DCI/NH<sub>3</sub>) m/e 447 (M + H)<sup>+</sup>. Analysis calcd for C<sub>27</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub>: C, 70.80; H, 6.70; N, 6.27. Found: C, 71.19; H, 6.86; N, 6.14.

**Example 56**

Preparation of [Cycloheptyl-(4-(2-quinolylmethoxy)phenyl)eth-2-yl]-2-iminoxy propionic acid.

25       The desired material was prepared according to the procedure of Example 55, except substituting 2-cycloheptyl-2-(4-(2-quinolylmethoxy)phenyl)acetic acid for 2-cyclohexyl-2-(4-(2-quinolylmethoxy)phenyl)acetic acid. m.p. 68-70 °C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.06 (m, 1H), 1.25 (m, 2H), 1.50 (m, 8H), 1.74 (s, 3H), 1.79 (m, 2H), 2.84 (q, 1H, J = 6 Hz), 4.36 (dd, 1H, J = 10 and 6 Hz), 4.47 (dd, 1H, J = 10 and 6 Hz), 5.33 (s, 2H), 6.98 (d, 2H, J = 9 Hz), 7.13 (d, 2H, J = 9 Hz), 7.62 (m, 1H), 7.68 (d, 1H, J = 9 Hz), 7.78 (m, 1H), 8.00 (t, 2H, J = 9 Hz), 8.42 (md, 1H, J = 9 Hz). MS (DCI/NH<sub>3</sub>) m/e 461 (M + H)<sup>+</sup>.

**Example 57**

Preparation of [2-chloro-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxy propionic acid.

Step 1: O-(2-chloro-4-(2-quinolylmethoxy) phenyl)methyloxime of pyruvic acid methyl ester.

5 To a solution of 2-chloro-4-(2-quinolylmethoxy)phenylmethanol (299 mg, 1.00 mmol) and triphenylphosphine (262 mg, 1.00 mmol) in THF (25 ml) was added dropwise at 0 °C under nitrogen a solution of DEAD (0.16 ml, 1.00 mmol) and after 10 min. a solution of oxime of methyl pyruvate (117 mg, 1.00 mmol) in THF (5 ml).  
10 The mixture was stirred at room temperature for 2 hours and then concentrated *in vacuo*. The residue was chromatographed (silica gel, hexane-ethyl acetate 3:1) to provide 190 mg of O-(2-chloro-4-(2-quinolylmethoxy) phenyl)methyloxime of pyruvic acid methyl ester.

15 Step 2: [2-chloro-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxy propionic acid.

A mixture of the O-(2-chloro-4-(2-quinolylmethoxy) phenyl)methyloxime of pyruvic acid methyl ester prepared in step 1, and 1N sodium hydroxide (1 ml) was stirred at room temperature for 2 hours and then concentrated *in vacuo*. To the residue was added water (20 ml) and the resulting solution was acidified with 10%  
20 citric acid to pH 3. The precipitated solid was filtered, dried *in vacuo* and crystallized from ethyl acetate-hexane to provide 150 mg of [2-chloro-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxy propionic acid. m.p. 169-170 °C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.94 (s, 3H), 5.22 (s, 2H), 5.42 (s, 2H), 7.07 (dd, 1H, J = 9 and 3 Hz), 7.25 (d, 1H, J = 3 Hz), 7.42 (d, 1H, J = 9 Hz), 7.63 (m, 1H),  
25 7.68 (d, 1H, J = 9 Hz), 7.80 (m, 1H), 8.00 (m, 2H), 8.42 (d, 1H, J = 9 Hz). MS (DCI/NH<sub>3</sub>) m/e 385 (M + H)<sup>+</sup>. Analysis calcd. for C<sub>20</sub>H<sub>17</sub>ClN<sub>2</sub>O<sub>4</sub>: C, 62.42; H, 4.45; N, 7.28. Found: C, 61.96; H, 4.10; N, 7.09.

**Example 58**

30 Preparation of [Cycloheptyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxy propionic acid.

The desired material was prepared according to the procedure of Example 2, except substituting cycloheptylmagnesium chloride for cyclohexylmagnesium chloride. m.p. 88-90 °C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.47 (m, 13H), 1.98  
35 (s, 3H), 5.00 (d, 1H, J = 9 Hz), 5.33 (s, 2H), 7.03 (d, 2H, J = 9 Hz), 7.21 (d, 2H, J = 9 Hz), 7.62 (m, 1H), 7.68 (d, 1H, J = 9 Hz), 7.78 (m, 1H), 8.01 (t, 2H, J = 9

Hz), 8.41 (d, 1H, J = 9 Hz). MS (DCI/NH<sub>3</sub>) m/e 447 (M + H)<sup>+</sup>. Analysis calcd. for C<sub>27</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub>·0.5 H<sub>2</sub>O: C, 71.18; H, 6.86; N, 6.15. Found: C, 71.35; H, 6.71; N, 6.07.

#### Example 59

5 Preparation of [Cyclohexyl-(4-(4-thiazolylmethoxy)phenyl)methyl]-2-iminoxy propionic acid.

The desired material was prepared according to the procedure of Example 2, except substituting 4-chloromethylthiazole for 2-chloromethylquinoline. m.p. 157 °C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.12 (m, 6H), 1.72 (m, 5H), 2.0 (s, 2H),  
10 4.93 (d, 1H, J = 9 Hz), 5.20 (s, 2H), 7.01 (d, 2H, J = 9 Hz), 7.18 (d, 2H, J = 9 Hz), 7.78 (d, 1H, J = 1.5 Hz), 9.13 (d, 1H, J = 1.5 Hz). MS (DCI/NH<sub>3</sub>) m/e 389 (M + H)<sup>+</sup>. Analysis calcd. for C<sub>20</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>S: C, 61.83; H, 6.23; N, 7.21. Found: C, 61.33; H, 6.26; N, 7.09.

#### Example 60

15 Preparation of [Cyclohexyl-(4-(4-thiazolylmethoxy)phenyl)methyl]iminoxacetic acid.

The desired material was prepared according to the procedure of Example 1, except substituting 2-chloromethylthiazole for 2-chloromethylquinoline. m.p. 159-160° C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.11 (m, 6H), 1.71 (m, 5H), 4.92 (d,  
20 1H, J = 9 Hz), 5.21 (s, 2H), 7.03 (d, 2H, J = 9 Hz), 7.19 (d, 2H, J = 9 Hz), 7.60 (s, 1H), 7.78 (d, 1H, J = 1.5 Hz), 9.13 (d, 1H, J = 1.5 Hz), 13.70 (broad s, 1H). MS (DCI/NH<sub>3</sub>) m/e 375 (M + H)<sup>+</sup>. Analysis calcd. for C<sub>19</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub>S: C, 60.94; H, 5.92; N, 7.48. Found: C, 61.17; H, 6.05; N, 7.40.

#### Example 61

25 Preparation of Sodium [Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypionate.

To a solution of cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl)-2-iminoxy propionic acid (300 mg; 0.69 mmol), prepared as in Example 2, in a mixture of THF  
30 and ethanol (15 ml, 1:1) at room temperature was added 1.0 N NaOH (0.69 ml; 0.69 mmol), and the resulting mixture was stirred at room temperature for 1 hour. The solvents were removed *in vacuo*, and the residue was diluted with water, at which point the desired material precipitated. The solid was filtered and washed several times with copious quantities of water. Some foaming occurred on filtration. The  
35 remaining solid was dried *in vacuo* for 5 hours to give 100 mg of Sodium [Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypionate as a white

powder. m.p. 138-150 °C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.02 (m, 5H), 1.36 (m, 1H), 1.61 (m, 4H), 1.84 (m, 1H), 1.89 (s, 3H), 4.74 (d, 1H, J = 9Hz), 5.34 (s, 2H), 7.0 (d, 2H, J = 9Hz), 7.13 (d, 2H, J = 9Hz), 7.62 (m, 1H), 7.68 (d, 1H, J = 9Hz), 7.79 (m, 1H), 8.0 (t, 2H, J = 9Hz), 8.40 (d, 1H, J = 9Hz). MS (FAB(+)) m/e 471 (M + K), (FAB(-)) m/e 431 (M - 1).

### Example 62

#### Preparation of (R)-[Cyclopentyl-(4-(2-quinolylmethoxy)phenyl)methyl]-E-2-iminoxypropionic acid.

##### 10 Step 1: 2-cyclopentyl-2-(4-(2-quinolylmethoxy) phenyl)acetic acid methyl ester.

To a mixture of 4-(2-quinolylmethoxy)phenylacetic acid methyl ester (6.36 g; 20.7 mmol) in DMF (10 ml) at 0°C was added in portions sodium hydride (60% dispersion in mineral oil) (840 mg; 21 mmol). The mixture was stirred at room temperature for 1 hour. It was then recooled to 0° C and cyclopentyl bromide (2.38  
15 ml, 22.0 mmol) was added dropwise. The resulting mixture was stirred at room temperature for 18 hours, and was then poured into water (50 ml). The product was extracted with ethyl acetate and purified by silica gel chromatography (hexane-ethyl acetate 3:1) to provide 5.5 g of 2-cyclopentyl-2-(4-(2-quinolylmethoxy) phenyl)acetic acid methyl ester.

20

##### Step 2: 2-cyclopentyl-2-(4-(2-quinolylmethoxy)phenyl)acetic acid.

To a solution of the 2-cyclopentyl-2-(4-(2-quinolylmethoxy) phenyl)acetic acid methyl ester prepared in step 1 in methanol (100 ml) was added dropwise 1N sodium hydroxide (25 ml) and the resulting mixture was refluxed at 50 °C for 16  
25 hours. The reaction mixture was then cooled to room temperature, and the methanol was removed *in vacuo*. The residue was acidified with 10% citric acid and the resulting solid was filtered, washed with water and dried *in vacuo* to provide 4.8 g of 2-cyclopentyl-2-(4-(2-quinolylmethoxy)phenyl)acetic acid.

##### 30 Step 3: 2-(R)- and (S)-cyclopentyl-2-(4-(2-quinolylmethoxy)phenyl)acetic acid (2-hydroxy-2-(S)-phenyl)eth-1-yl amide.

To a solution of 2-cyclopentyl-2-(4-(2-quinolylmethoxy)phenyl)acetic acid (4.73 g, 13.1 mmol), prepared as in step 2, and (S)-phenylglycinol (2.17 g, 15.8 mmol) in DMF (65 ml) at -10 to -15°C was added dropwise a solution of  
35 diphenylphosphoryl azide (3.51 ml, 15.8 mmol) in DMF (15 ml) followed by addition of triethylamine (4.4 ml, 31.6 mmol). The mixture was stirred at that



temperature for 16 hours. The reaction mixture was then poured into ice-water, and the precipitated solid was filtered, washed with water and dried *in vacuo*.

Crystallization three times from ethanol gave 1.9 g of 2-(R)-cyclopentyl-2-(4-(2-quinolylmethoxy)phenyl)acetic acid (2-hydroxy-1-(S)-phenyl)eth-1-yl amide. The  
5 mother liquors were concentrated and recrystallized from methylene chloride (three times) to provide 1.3 g of 2-(S)-cyclopentyl-2-(4-(2-quinolylmethoxy)phenyl)acetic acid (2-hydroxy-2-(S)-phenyl)eth-1-yl amide.

Step 4: 2-(R)-cyclopentyl-2-(4-(2-quinolylmethoxy)phenyl)acetic acid.

10 A mixture of (R) cyclopentyl-2-(4-(2-quinolylmethoxy)phenyl)acetic acid (2-hydroxy-1-(S)-phenyl)eth-1-yl amide (1.87 g, 3.9 mmol), prepared as in step 3, and 20 ml of 5N sulfuric acid in dioxane (20 ml) was refluxed for 24 hours. The reaction mixture was then cooled to room temperature and pH was adjusted to 3 by addition of 2N sodium hydroxide. The solid was filtered, washed with water, dried *in vacuo*, and  
15 crystallized from ethanol to afford 800 mg of 2-(R)-cyclopentyl-2-(4-(2-quinolylmethoxy)phenyl)acetic acid. The SS-diastereoisomer (1.35 g, 2.8 mmol) and 5N sulfuric acid (15 ml) in dioxane (15 ml) was refluxed for 24 hours. Work-up as above afforded 600 mg of 2-(S)-cyclopentyl-2-(4-(2-quinolylmethoxy)phenyl)acetic acid.

20

Step 5: 2-(R)-cyclopentyl-2-(4-(2-quinolylmethoxy) phenyl)ethan-1-ol.

To a solution of 2-(R)-cyclopentyl-2-(4-(2-quinolylmethoxy)phenyl)acetic acid (290 mg, 0.8 mmol), prepared as in step 4, and triethylamine (0.14 ml, 1.0 ml) in THF (35 ml) at -25 °C was added dropwise ethyl chloroformate (0.1 ml, 1.0  
25 mmol). Upon completion of addition, the mixture was stirred for 15 min. and warmed to 0° C. Sodium borohydride (150 mg, 4.0 mmol) was added followed by very slow addition of methanol (15 ml). The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The residue was  
30 chromatographed (silica gel, hexane-ethyl acetate 2:1) to afford 180 mg of 2-(R)-cyclopentyl-2-(4-(2-quinolylmethoxy) phenyl)ethan-1-ol.

Step 6: N-phthaloyl-O-(2-(R)-cyclopentyl-2-(4-(2-quinolylmethoxy) phenyl)eth-1-yl) hydroxylamine.

35 To a solution of 2-(R)-cyclopentyl-2-(4-(2-quinolylmethoxy) phenyl)ethan-1-ol (180 mg, 0.51 mmol), prepared in step 5, triphenylphosphine (262 mg, 1.00

mmol) and *N*-hydroxyphthalimide (85 mg, 0.52 mmol) in THF (30 ml) was added dropwise a solution of DEAD (0.16 ml, 1.0 mmol) in THF (5 ml), and the reaction mixture was left at room temperature for 12 hours. The mixture was concentrated *in vacuo* and the residue was chromatographed (silica gel, hexane-ethyl acetate 2:1) to give 240 mg of *N*-phthaloyl-*O*-(2-(*R*)-cyclopentyl-2-(4-(2-quinolylmethoxy)phenyl)eth-1-yl) hydroxylamine.

Step 7: *O*-(2-(*R*)-cyclopentyl-2-(4-(2-quinolylmethoxy)phenyl)eth-1-yl) hydroxylamine.

A mixture of *N*-phthaloyl-*O*-(2-(*R*)-cyclopentyl-2-(4-(2-quinolylmethoxy)phenyl)eth-1-yl) hydroxylamine (200 mg, 0.41 mmol), prepared in step 7, and hydrazine hydrate (0.06 ml, 1.0 mmol) in ethanol (15 ml) was refluxed for 30 min. 10% aqueous Na<sub>2</sub>CO<sub>3</sub> was added and the mixture was extracted with ethyl acetate to afford 130 mg of *O*-(2-(*R*)-cyclopentyl-2-(4-(2-quinolylmethoxy)phenyl)eth-1-yl) hydroxylamine.

Step 8: *O*-(2-(*R*)-cyclopentyl-2-(4-(2-quinolylmethoxy)phenyl)eth-1-yl)oxime of propionic acid methyl ester.

To a mixture of the *O*-(2-(*R*)-cyclopentyl-2-(4-(2-quinolylmethoxy)phenyl)eth-1-yl) hydroxylamine prepared in step 7 in dioxane-methanol (1:1, 30 ml) were added methyl pyruvate (0.1 ml, 1.0 mmol) and acetic acid (0.03 ml, 0.5 mmol), and the resulting mixture was stirred at room temperature for 12 hours. The organics were removed *in vacuo*, and the residue was dissolved in ethyl acetate. The organic phase was washed with water, 10% sodium bicarbonate, and brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The residue was chromatographed (silica gel, hexane-ethyl acetate 3:1) to afford 30 mg of *O*-(2-(*R*)-cyclopentyl-2-(4-(2-quinolylmethoxy)phenyl)eth-1-yl)oxime of pyruvic acid methyl ester.

Step 9: (*R*)-[Cyclopentyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*E*-2-iminoxypropionic acid.

To a solution of the *O*-(2-(*R*)-cyclopentyl-2-(4-(2-quinolylmethoxy)phenyl)eth-1-yl)oxime of pyruvic acid methyl ester prepared in step 8 in dioxane-methanol (1:1, 10 ml) was added 1*N* sodium hydroxide (0.1 ml), and the mixture was stirred at 50° C for 2 hours. The reaction mixture was then concentrated *in vacuo*, and the residue was diluted with water (5 ml) and acidified to pH 3. Extraction with ethyl acetate afforded 20 mg of (*R*)-[Cyclopentyl-(4-(2-

quinolylmethoxy)phenyl)methyl]-E-2-iminoxypropionic acid. m.p 60-62 °C,  $\alpha_D = -25.5$  ( $c = 2.2$ ,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.03 (m, 1H), 1.26 (m, 1H), 1.57 (m, 5H), 1.90 (s+m, 4H), 2.10 (m, 1H), 2.70 (m, 1H), 4.38 (dd, 1H,  $J = 10$  and 7 Hz), 4.50 (dd, 1H,  $J = 10$  and 4 Hz), 5.38 (s, 2H), 6.94 (d, 2H,  $J = 9$  Hz), 7.08 (d, 2H,  $J = 9$  Hz), 7.55 (m, 1H), 7.70 (m, 2H), 7.83 (m, 1H), 8.09 (d, 1H,  $J = 9$  Hz), 8.20 (d, 1H,  $J = 9$  Hz). MS (DCI/ $\text{NH}_3$ )  $m/e$  433 ( $M + H$ )<sup>+</sup>. Analysis calc'd for  $\text{C}_{26}\text{H}_{28}\text{N}_2\text{O}_4$ : C, 72.20; H, 6.53; N, 6.48. Found: C, 72.22; H, 6.76; N, 6.46.

### Example 63

#### 10 Preparation of (S)-[Cyclopentyl-(4-(2-quinolylmethoxy)phenyl)methyl]-E-2-iminoxypropionic acid.

The desired material was prepared according to the procedure of Example 62, steps 4-9, except substituting 2-(S)-cyclopentyl-2-(4-(2-quinolylmethoxy)phenyl)acetic acid for 2-(R)-cyclopentyl-2-(4-(2-quinolylmethoxy)phenyl)acetic acid. m.p 63-65 °C.  $\alpha_D = +23.7$  ( $c = 1.9$ ,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.00 (m, 1H), 1.25 (m, 1H), 1.57 (m, 5H), 1.89 (s+m, 4H), 2.05 (m, 1H), 2.68 (m, 1H), 4.35 (m, 1H), 4.49 (m, 1H), 5.36 (s, 2H), 6.93 (d, 2H,  $J = 9$  Hz), 7.06 (d, 2H,  $J = 9$  Hz), 7.55 (m, 1H), 7.70 (m, 2H), 7.82 (m, 1H), 8.09 (d, 1H,  $J = 9$  Hz), 8.20 (d, 1H,  $J = 9$  Hz). MS (DCI/ $\text{NH}_3$ )  $m/e$  433 ( $M + H$ )<sup>+</sup>. Analysis calc'd for  $\text{C}_{26}\text{H}_{28}\text{N}_2\text{O}_4$ : C, 72.20; H, 6.53; N, 6.48. Found: C, 72.22; H, 6.76; N, 6.46.

### Example 64

#### Preparation of [Cyclohexyl-(4-(2-quinolylmethoxy)benzof[b]thien-2-yl)methyl]-2-iminoxypropionic acid.

#### 25 Step 1: 2-nitro-5-(2-quinolylmethoxy)benzyl alcohol.

A mixture of 5-hydroxy-2-nitrobenzyl alcohol (5.1 g, 30 mmol), tetraethylammonium fluoride hydrate (8.94g, 60 mmol) and 2-chloromethylquinoline (5.31 g, 30 mmol) in DMF (90 ml) was stirred at room temperature for 72 hours. The reaction mixture was then poured into water and extracted with ethyl acetate. The extract was dried over  $\text{MgSO}_4$  and concentrated *in vacuo*. To the residue was added methylene chloride (25 ml) and the solid was filtered to provide 3.1 g of 2-nitro-5-(2-quinolylmethoxy)benzyl alcohol.

#### Step 2: 2-nitro-5-(2-quinolylmethoxy)benzaldehyde.

35 To a solution of 2-nitro-5-(2-quinolylmethoxy)benzyl alcohol (1.74 g, 5.6 mmol), prepared in step 1, and dicyclohexylcarbodiimide (3.71 g, 18 mmol) in

DMSO (25 ml) was added 1M solution of phosphoric acid in DMSO (2.7 ml), and the resulting mixture was stirred at room temperature for 1 hour. Ethyl acetate (100 ml) was then added and the precipitated dicyclohexylurea was filtered off. The filtrate was washed with water, and brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*.

- 5 The residue was chromatographed (silica gel, methylene chloride-ethyl acetate 15:1) to afford 1.25 g of 2-nitro-5-(2-quinolylmethoxy)benzaldehyde.

Step 3: ethyl 5-(2-quinolylmethoxy)benzo[b]thiophene-2-carboxylate.

- To a solution of 2-nitro-5-(2-quinolylmethoxy)benzaldehyde (1.24 g, 4 mmol), prepared in step 2, and potassium carbonate (700 mg, 5.0 mmol) in DMF (15 ml) was added dropwise ethyl thioglycolate (0.46 ml, 4.0 mmol), and the resulting mixture was stirred at room temperature for 16 hours. The reaction mixture was then poured into ice-water and extracted with ethyl acetate. The organic extract was washed with water, and brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The residue was chromatographed (silica gel, methylene chloride-ethyl acetate 24:1) to provide 480 mg of ethyl 5-(2-quinolylmethoxy)benzo[b]thiophene-2-carboxylate.

Step 4: 5-(2-quinolylmethoxy)benzo[b]thiophene-2-carboxylic acid.

- A mixture of ethyl 5-(2-quinolylmethoxy)benzo[b]thiophene-2-carboxylate (472 mg; 1.3 mmol), prepared as in step 3, and 1N sodium hydroxide (1.5 ml, 1.5 mmol) in dioxane (15 ml) and methanol (10 ml) was stirred at room temperature for 8 hours. The organics were then removed *in vacuo* and the residue was acidified to pH 3 to provide 440 mg of 5-(2-quinolylmethoxy)benzo[b]thiophene-2-carboxylic acid.

- 25 Step 5: 5-(2-quinolylmethoxy)benzo[b]thiophene-2-carboxylic acid N-methyl-O-methyl amide.

- To a mixture of 5-(2-quinolylmethoxy)benzo[b]thiophene-2-carboxylic acid (440 mg, 1.3 mmol), prepared in step 4, N-methyl-O-methylhydroxylamine hydrochloride (146 mg, 1.5 mmol), pyridine (0.122 ml, 1.5 mmol) and carbon tetrabromide (497 mg, 1.5 mmol) in methylene chloride (25 ml) and THF (15 ml) was added triphenylphosphine (393 mg, 1.5 mmol) in portions. The mixture was stirred at room temperature for 60 min and concentrated *in vacuo*. The residue was chromatographed (methylene chloride-ethyl acetate 9:1) to afford 470 mg of 5-(2-quinolylmethoxy)benzo[b]thiophene-2-carboxylic acid N-methyl-O-methyl amide.

Step 6: 5-(2-quinolylmethoxy)benzo[b]thiophene-2-carbaldehyde.

To a solution of 5-(2-quinolylmethoxy)benzo[b]thiophene-2-carboxylic acid *N*-methyl-*O*-methyl amide (470 mg; 1.26 mmol), prepared in step 5, in THF (20 ml) at -78 °C was added 1*N* DIBAL in THF (1.5 ml, 1.5 mmol). The reaction mixture was stirred at room temperature for 18 hours, and an additional 1.5 mL of DIBAL was added. The reaction mixture was stirred for 15 hours and 3 mL of DIBAL was added. After stirring for 12 hours, the reaction was quenched with saturated aqueous NH<sub>4</sub>Cl. The mixture was extracted with ethyl acetate, and the organic phase was dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was chromatographed (silica gel, methylene chloride-ethyl acetate 9:1) to give 100 mg of 5-(2-quinolylmethoxy)benzo[b]thiophene-2-carbaldehyde.

Step 7: *O*-(cyclohexyl)-(4-(2-quinolylmethoxy)benzo[b]thienyl)methyl]hydroxylamine.

The desired compound was prepared according to the method of Example 1, steps 2-4, except substituting 5-(2-quinolylmethoxy)benzo[b]thiophene-2-carbaldehyde, prepared as in step 6, for 4-(2-quinolylmethoxy)benzaldehyde.

Step 8: [Cyclohexyl-(4-(2-quinolylmethoxy)benzo[b]thien-2-yl)methyl]-2-iminoxypropionic acid.

The desired material was prepared according to the procedure of Example 2, except substituting *O*-(cyclohexyl)-(4-(2-quinolylmethoxy)benzo[b]thienyl)methyl]hydroxylamine for *O*-(cyclohexyl)-(4-(2-quinolylmethoxy)phenyl)methyl]hydroxylamine. m.p. 91-93 °C (methanol-water). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 1.18 (m, 6H), 1.44 (m, 1H), 1.63 (m, 3H), 1.92 (m, 1H), 2.00 (s, 3H), 5.30 (d, 1H, *J* = 7 Hz), 5.43 (s, 2H), 7.11 (d-d, 1H, *J* = 9 and 3 Hz), 7.25 (s, 1H), 7.48 (d, 1H, *J* = 3 Hz), 7.62 (m, 1H), 7.70 (d, 1H, *J* = 9 Hz), 7.80 (m, 2H), 8.01 (m, 2H), 8.42 (d, 1H, *J* = 9 Hz), 13.05 (broad s, 1H). MS (DCI/NH<sub>3</sub>) *m/e* 489 (M + H)<sup>+</sup>.

**Example 65**

Preparation of [Cyclohexyl-(6-(2-quinolylmethoxy)pyrid-3-yl)methyl]iminoxy acetic acid.

Step 1: 6-hydroxynicotinic acid methyl ester.

To a suspension of 6-hydroxynicotinic acid (20.0 g, 0.144 mol) in methanol (350 ml) at room temperature was added concentrated sulfuric acid (9.98 ml, 0.179 mol) and the mixture was refluxed with vigorous stirring for 16 hours. Much of the

organic solvent was removed *in vacuo*. The remaining residue was neutralized with saturated aqueous NaHCO<sub>3</sub>, and the product was extracted from the aqueous phase with ethyl acetate. The organic layer was dried over MgSO<sub>4</sub> and concentrated *in vacuo* to give 11.50 g of 6-hydroxynicotinic acid methyl ester as a creamish powder.

5

Step 2: 6-(quinol-2-ylmethoxy)nicotinic acid methyl ester.

To a solution of 6-hydroxynicotinic acid methyl ester (10.0g, 0.0652 mol), prepared as in step 1, in DMF (350 ml) at room temperature was added anhydrous K<sub>2</sub>CO<sub>3</sub> (19.0 g, 0.137 mol) followed by 2-chloromethylquinoline hydrochloride (14.0 g, 0.0652 mol), and the mixture was allowed to stir at room temperature overnight. Once the starting material was consumed, water (700 ml) was added to the mixture, and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The resulting white precipitate was filtered and washed with hexanes to give 15.20 g of 6-(quinol-2-ylmethoxy)nicotinic acid methyl ester.

15

Step 3: 6-(2-quinolylmethoxy)nicotinic acid.

To a solution of 6-(quinol-2-ylmethoxy)nicotinic acid methyl ester ( 5.06 g, 17.2 mmol), prepared as in step 2, in methanol (100 ml) at room temperature with stirring was added 1N NaOH ( 18.9 ml, 18.9 mmol). The resulting mixture was allowed to stir at room temperature for 14 hours. The mixture was then refluxed for 3 hours, cooled to room temperature and concentrated *in vacuo*. The residue was diluted with water and the aqueous layer was extracted with ethyl acetate. The aqueous layer was acidified to pH 3 with 10% citric acid to give a white precipitate. The precipitate was filtered and washed with water and diethyl ether. The solid was dried overnight at 80 °C under reduced pressure to give 4.46 g of 6-(2-quinolylmethoxy)nicotinic acid.

20

25

Step 4: 6-(2-quinolylmethoxy)pyrid-3-ylmethanol.

To a solution of 6-(2-quinolylmethoxy)nicotinic acid (4.38g, 1.56 mmol), prepared as in step 3, and triethylamine (0.228 ml, 1.64 mmol) in THF (80 ml) at -10 °C to -5 °C was added dropwise a solution of ethyl chloroformate (1.57 ml, 1.64 mmol) in THF (5 ml), and the reaction mixture was stirred at 0° C for 1 hour. Precipitated triethylamine hydrochloride was filtered and washed with THF. The combined filtrate and washings were placed in an addition funnel and added dropwise to a mixture of sodium borohydride (1.50g, 3.91 mmol) in water (20 ml) at 0° C.

30

35

When the bubbling ceased, the mixture was allowed to warm to room temperature and stir for 2 hours. 10% Citric acid added to bring the mixture to pH 3 and the aqueous layer was extracted with ethyl acetate. The organic extract was washed with 1 N NaOH, water, and brine, and dried over MgSO<sub>4</sub>. The solvent was removed *in vacuo* and the residue treated with ethyl acetate-hexane to precipitate the product, 3.44 g of 6-(2-quinolylmethoxy)pyrid-3-ylmethanol.

Step 5: 6-(2-quinolylmethoxy)pyrid-3-yl carboxaldehyde.

To a solution of oxalyl chloride (0.363 ml, 4.13 mmol) in methylene chloride (10 ml) at -65°C was added dropwise DMSO (0.587 ml, 8.27 mmol), and mixture was stirred for 5 minutes. Then 6-(2-quinolylmethoxy)pyrid-3-ylmethanol (1.00 g; 2.76 mmol), prepared as in step 4, was added slowly. After 15 minutes, triethylamine (2.62 ml, 18.8 mmol) was added and stirring was continued for an additional 10 minutes. The reaction was warmed slowly to room temperature and quenched with brine. The aqueous layer was extracted with methylene chloride. The organic layer was dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was precipitated with ethyl acetate and filtered to give 6-(2-quinolylmethoxy)pyrid-3-yl carboxaldehyde (990 mg).

Step 6: cyclohexyl-(6-(quinolin-2-ylmethoxy)pyridin-3-yl)-methanol.

A solution of 6-(2-quinolylmethoxy)pyrid-3-yl carboxaldehyde (0.979 g; 3.71 mmol), prepared as in step 5, in anhydrous THF (15 ml) was cooled to -78°C and cyclohexylmagnesium chloride (2 M sol'n, 3.89 ml, 7.79 mmol) was added dropwise via syringe. After 3 hours, the reaction mixture was allowed to warm to room temperature and stir for an additional hour. Saturated aqueous NH<sub>4</sub>Cl was added to the mixture and the organics were removed *in vacuo*. The aqueous layer was extracted with ethyl acetate. The organic extract was washed with 10% citric acid, water, and brine, dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (chloroform followed by 5% methanol in chloroform) to afford 297 mg of cyclohexyl-(6-(quinolin-2-ylmethoxy)pyridin-3-yl)-methanol.

Step 7: *N*-phthaloyl-*O*-(cyclohexyl-(6-(2-quinolylmethoxy)pyrid-3-yl)methyl)hydroxylamine.

To a solution of cyclohexyl-(6-(quinolin-2-ylmethoxy)pyridin-3-yl)-methanol (0.243 g, 0.689 mmol), prepared as in step 6, triphenylphosphine (0.363 g, 1.38 mmol), and *N*-hydroxyphthalimide (0.123 g, 0.759 mmol) in anhydrous THF (10 ml) under nitrogen at 0° C was added diethyl azodicarboxylate (0.217 ml, 1.38 mmol) in THF (10 ml) over a one hour. The mixture was then allowed to warm to room temperature and stir for 2 hours. The solvent was removed *in vacuo* and the residue was subjected to silica gel flash chromatography (1% acetic acid in ethyl acetate-hexane 4:1, followed by 5% acetic acid in ethyl acetate-hexane 4:1) to give a mixture of the desired *N*-phthaloyl-*O*-(cyclohexyl-(6-(2-quinolylmethoxy)pyrid-3-yl)methyl)hydroxylamine and triphenylphosphine oxide (230 mg total material).

Step 8: *O*-(cyclohexyl-(6-(2-quinolylmethoxy)pyrid-3-yl)methyl) hydroxylamine.

The above crude *N*-phthaloyl-*O*-(cyclohexyl-(6-(2-quinolylmethoxy)pyrid-3-yl)methyl)hydroxylamine (0.205 g, 0.416 mmol), prepared in step 7, was dissolved in a mixture of methylene chloride and ethanol (1:1, 4 ml) and was treated with hydrazine hydrate (0.05 ml, 1.04 mmol) for one hour at reflux. The mixture was cooled to room temperature and 10% aqueous Na<sub>2</sub>CO<sub>3</sub> was added to dissolve precipitated solid. The aqueous layer was extracted with ethyl acetate. The organic extract was washed with water and brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo* to provide *O*-(cyclohexyl-(6-(2-quinolylmethoxy)pyrid-3-yl)methyl) hydroxylamine which was used without further purification.

Step 9: [Cyclohexyl-(6-(2-quinolylmethoxy)pyrid-3-yl)methyl]iminoxy acetic acid.

A mixture of *O*-(cyclohexyl-(6-(2-quinolylmethoxy)pyrid-3-yl)methyl) hydroxylamine (0.198 g, 0.545 mmol), prepared in step 8, sodium acetate trihydrate (0.074 g, 0.545 mmol) and glyoxylic acid (0.055 g, 0.60 mmol) in ethanol-dioxane-water (2:1:1, 4 ml) was allowed to stir at room temperature overnight. The solvent was then removed *in vacuo*, and the residue was treated with 15% NaOH and extracted with ethyl acetate. The aqueous layer was acidified with 10% citric acid to pH 3 and extracted with ethyl acetate. The organic layer was then dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was treated with diethyl ether and the resulting precipitate was filtered and washed with diethyl ether to afford 60 mg of [Cyclohexyl-(6-(2-quinolylmethoxy)pyrid-3-yl)methyl]iminoxy acetic acid as a white powder. m.p. 175 -178 °C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 0.88-1.32 (m, 5H),



1.46-1.56 (m, 1H), 1.58-1.87 (m, 4H), 1.90-2.0 (m, 1H), 4.78 (d, 1H, J = 9 Hz), 5.30-5.47 (m, 2H), 6.43 (d, 1H, J = 9 Hz), 7.38 (d, 1H, J = 9 Hz), 7.43 (dd, 1H, J = 9, 3 Hz), 7.53-7.62 (m, 2H), 7.69-7.77 (m, 1H), 7.78-7.86 (m, 2H), 7.95 (dd, 1H, J = 9, 3 Hz), 8.33 (d, 1H, J = 9 Hz), 13.23 (br s, 1H). MS (DCI/NH<sub>3</sub>) m/e 420 (M + H)<sup>+</sup>. Analysis calculated for: C<sub>24</sub>H<sub>25</sub>N<sub>3</sub>O<sub>4</sub>·0.30 H<sub>2</sub>O: C, 67.85; H, 6.07; N, 9.89. Found: C, 67.83; H, 6.28; N, 9.49.

### Example 66

#### Preparation of [Cyclohexyl-(4-(2-benzothiazolylmethoxy)phenyl)methyl]liminooxyacetic acid.

The desired material was prepared according to the procedure of Example 1, except substituting 2-chloromethylbenzothiazole for 2-chloromethylquinoline. m.p. 179 °C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.05 (m, 6H), 1.75 (m, 5H), 4.91 (d, 1H, J = 9 Hz), 5.60 (s, 2H), 7.08 (d, 2H, J = 9 Hz), 7.21 (d, 2H, J = 9 Hz), 7.50 (m, 3H), 8.02 (m, 1H), 8.13 (m, 1H). MS (DCI/NH<sub>3</sub>) m/e 425 (M + H)<sup>+</sup>. Analysis calcd. for C<sub>23</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>S: C, 65.06; H, 5.70; N, 6.59. Found: C, 65.78; H, 5.78; N, 6.37.

### Example 67

#### Preparation of [Cyclohexyl-(4-(6-(4-fluorophenoxy)pyrid-2-ylmethoxy)phenyl)methyl]liminooxyacetic acid.

The desired material was prepared according to the procedure of Example 2, except substituting 4-(6-(4-fluorophenoxy)pyrid-2-ylmethoxy)benzaldehyde for 4-(2-quinolylmethoxy)benzaldehyde. m.p. 54-57 °C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.10 (m, 5H), 1.35 (m, 1H), 1.70 (m, 5H), 1.99 (s, 3H), 4.91 (d, 1H, J = 7 Hz), 4.98 (s, 2H), 6.94 (m, 3H), 7.20 (m, 7H), 7.88 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 510 (M + NH<sub>4</sub>)<sup>+</sup>, 493 (M + H)<sup>+</sup>.

### Example 68

#### Preparation of [Cyclohexyl-(4-(1-methyl-2-benzimidazolylmethoxy)phenyl)methyl]-2-iminooxypropionic acid.

The desired material was prepared according to the procedure of Example 2, except substituting 2-chloromethyl-1-methylbenzimidazole for 2-chloromethylquinoline. mp. 190-192 °C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.10 (m, 5H), 1.35 (m, 1H), 1.71 (m, 5H), 1.97 (s, 3H), 3.86 (s, 3H), 4.92 (d, 1H, J = 7 Hz), 5.38 (s, 2H), 7.10 (d, 2H, J = 9 Hz), 7.24 (m, 4H), 7.58 (d, 1H, J = 9 Hz), 7.65 (d, 1H, J = 9 Hz), 12.88 (broad s, 1H). MS DCI/NH<sub>3</sub>) m/e 436 (M + H)<sup>+</sup>.

Analysis calcd. for  $C_{25}H_{29}N_3O_4$ : C, 68.95; H, 6.71; N, 9.65. Found: C, 68.49; H, 6.71; N, 9.56.

### Example 69

#### Preparation of [Cyclohexyl-(4-(2-benzoxazolylmethoxy)phenyl)methyl] iminoxvacetic acid.

5 The desired material was prepared according to the procedure of Example 1 substituting 2-chloromethylbenzoxazole for 2-chloromethylquinoline, mp. 112°C;  $^1H$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$ : 1.08 (m, 6H), 1.73 (m, 5H), 4.90 (d, 2H, J = 9 Hz), 5.45 (s, 2H), 7.05 (d, 2H, J = 9 Hz), 7.21 (d, 2H, J = 9 Hz), 7.43 (m, 2H),  
10 7.55 (s, 1H), 7.80 (m, 2H), 13.25 (broad s, 1H); MS (DCI/ $NH_3$ ) m/e: 409 (M + 1); Analysis calcd. for  $C_{23}H_{24}N_2O_5 \times 0.5 H_2O$ : C, 66.17; H, 5.98; N, 6.71; Found: C, 66.50; H, 6.09; N, 6.90.

### Example 70

#### Preparation of [Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxy propionic acid 2-thiazolylamide.

15 To a solution of [cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypropionic acid (207 mg, 0.48 mmol), prepared as in Example 2, in THF (15 ml) at 0 °C was added triethylamine (0.20 ml, 1.40 mmol) followed by dropwise addition of methanesulfonyl chloride (0.074 ml, 0.96 mmol). Upon completion of  
20 addition, the reaction was stirred for 10 min and then dimethylaminopyridine (117 mg, 0.96 mmol) was added to the reaction mixture. After an additional 10 min., 2-aminothiazole (58 mg, 0.575 mmol) was added, and the reaction was allowed to warm to room temperature. The reaction was left at ambient temperature for 12 hours, and then was concentrated *in vacuo*. To the residue was added water and the  
25 resulting solution was extracted with methylene chloride. The organic layer was then washed with brine, dried over  $MgSO_4$ , and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (hexane-ethyl acetate 2:1) to give 80 mg of [Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxy propionic acid 2-thiazolylamide as a white powder. m.p. 61-65 °C.  $^1H$   
30 NMR (300 MHz, DMSO- $d_6$ )  $\delta$ : 1.10 (m, 5H), 1.38 (m, 1H), 1.66 (m, 3H), 1.89 (m, 2H), 2.06 (s, 3H), 5.06 (d, 1H, J = 9 Hz), 5.35 (s, 2H), 7.04 (d, 2H, J = 9 Hz), 7.25 (m, 3H), 7.51 (d, 1H, J = 3 Hz), 7.62 (m, 1H), 7.67 (d, 1H, J = 9 Hz), 7.78 (m, 1H), 8.0 (t, 2H, J = 9 Hz), 8.40 (d, 1H, J = 9 Hz), 11.67 (s, 1H). MS (DCI/ $NH_3$ ) m/e 515 (M + H) $^+$ . Analysis calcd. for  $C_{29}H_{30}N_4O_3S$ : C, 67.68; H, 5.88; N, 10.89. Found: C, 67.60; H, 5.91; N, 10.40.  
35

**Example 71**Preparation of [Cyclohexyl-(4-(2-quinolinylmethoxy)phenyl)methyl]-2-iminoxypropionic acid 2-pyridylamide.

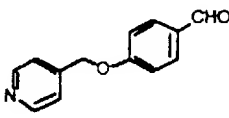
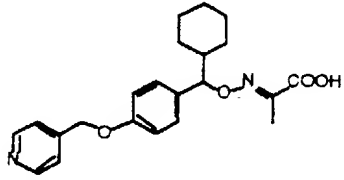
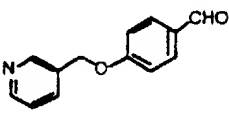
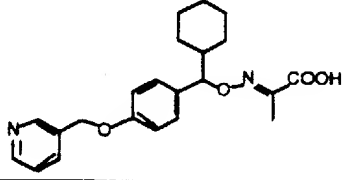
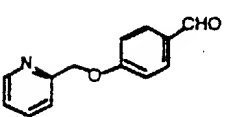
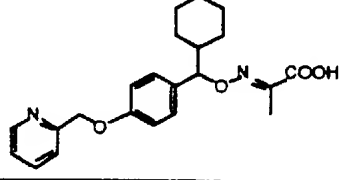
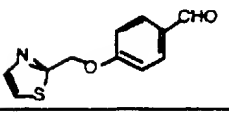
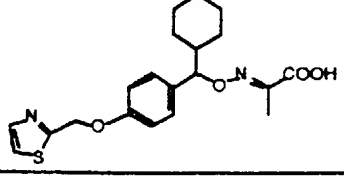
To a solution of [cyclohexyl-(4-(2-quinolinylmethoxy)phenyl)methyl]-2-iminoxypropionic acid (200 mg, 0.46 mmol), prepared as in Example 2, and triethylamine (0.13 ml, 0.93 mmol) in THF (5 ml) at 0 °C was added dropwise methanesulfonyl chloride (0.04 ml, 0.51 mmol). Upon completion of addition, the reaction mixture was stirred at 0 °C for 1.3 hours. A solution of 2-aminopyridine (50 mg, 0.56 mmol) and DMAP (110 mg, 0.93 mmol) in THF (5 ml) was added, the cooling bath was withdrawn and the reaction was allowed to warm to room temperature. The mixture was left at ambient temperature for 12 hours. The reaction was quenched with water and extracted with ethyl acetate (2x50 ml). The organic layer was washed with water and brine, dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (hexane-ethyl acetate 2:1) to afford 161 mg of [Cyclohexyl-(4-(2-quinolinylmethoxy)phenyl)methyl]-2-iminoxypropionic acid 2-pyridylamide as a white powder. m.p. 49-54 °C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.06 (m, 5H), 1.38 (m, 1H), 1.66 (m, 3H), 1.84 (m, 2H), 2.06 (s, 3H), 5.05 (d, 1H, J = 9 Hz), 5.35 (s, 2H), 7.06 (d, 2H, J = 9 Hz), 7.15 (m, 1H), 7.25 (d, 2H, J = 9 Hz), 7.61 (m, 1H), 7.67 (d, 1H, J = 9 Hz), 7.80 (m, 2H), 8.01 (m, 3H), 8.31 (m, 1H), 8.39 (d, 1H, J = 9 Hz), 9.30 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 509 (M + H)<sup>+</sup>. Analysis calcd. for C<sub>31</sub>H<sub>32</sub>N<sub>4</sub>O<sub>3</sub>: C, 73.21; H, 6.34; N, 11.02. Found: C, 73.02; H, 6.32; N, 10.87.

**Example 72**Preparation of [Cyclohexyl-(4-(2-quinolinylmethoxy)phenyl)methyl]-2-iminoxypropionic acid 5-tetrazylamide.

The desired material was prepared according to the procedure of Example 71, except substituting 5-aminotetrazole for 2-aminopyridine and by adding a small amount of DMF (2 ml) to solublize the 5-aminotetrazole. m.p. 180-184 °C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.07 (m, 5H), 1.39 (m, 1H), 1.66 (m, 3H), 1.91 (m, 2H), 2.05 (s, 3H), 5.05 (d, 1H, J = 9 Hz), 5.35 (s, 2H), 7.05 (d, 2H, J = 9 Hz), 7.25 (d, 2H, J = 9 Hz), 7.61 (m, 1H), 7.67 (d, 1H, J = 9 Hz), 7.78 (m, 1H), 8.0 (t, 2H, J = 9 Hz), 8.40 (d, 1H, J = 9 Hz), 11.30 (br s, 1H). MS (DCI/NH<sub>3</sub>) m/e 500 (M + H)<sup>+</sup>. Analysis calcd. for C<sub>27</sub>H<sub>29</sub>N<sub>7</sub>O · 1.20H<sub>2</sub>O: C, 62.22; H, 6.07; N, 18.81. Found: C, 61.99; H, 5.76; N, 18.75.

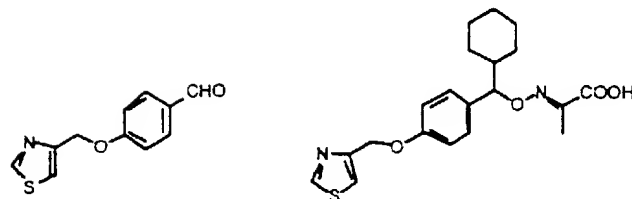
The examples shown in Table 4 are prepared in a manner analogous to that of Example 2 substituting the requisite aldehyde prepared by known literature methods and the requisite organometallic reagent for addition reaction to the aldehyde shown to provide the final product examples illustrated.

Table 4.

Example	Aldehyde	Final Product
73		
	[Cyclohexyl-(4-(4-pyridylmethoxy)phenyl)methyl]-2-iminoxypropionic acid	
74		
	[Cyclohexyl-(4-(3-pyridylmethoxy)phenyl)methyl]-2-iminoxypropionic acid	
75		
	[Cyclohexyl-(4-(2-pyridylmethoxy)phenyl)methyl]-2-iminoxypropionic acid	
76		
	[Cyclohexyl-(4-(2-thiazolylmethoxy)phenyl)methyl]-2-iminoxypropionic acid	

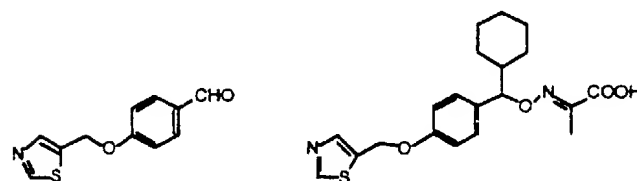
72

77



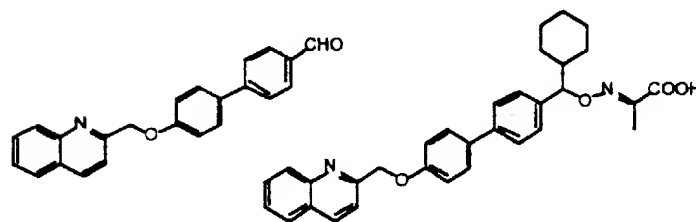
[Cyclohexyl-(4-(4-thiazolylmethoxy)phenyl)methyl]-2-iminoxypropionic acid

78



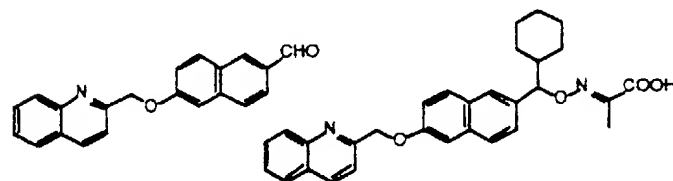
[Cyclohexyl-(4-(5-thiazolylmethoxy)phenyl)methyl]-2-iminoxypropionic acid

79



[Cyclohexyl-(4-(2-quinolylmethoxy)phenyl-4-phenyl)methyl]-2-iminoxypropionic acid

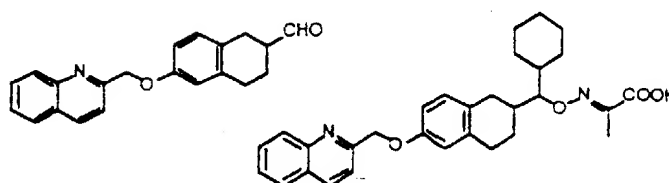
80



[Cyclohexyl-(6-(2-quinolylmethoxy)naphth-2-yl)methyl]-2-iminoxypropionic acid

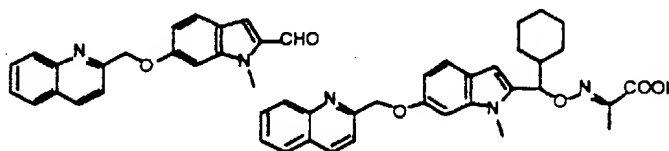
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81



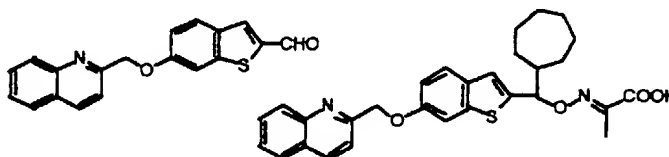
[Cyclohexyl-(6-(2-quinolylmethoxy)-1,2,3,4-tetrahydronaphth-2-yl)methyl]-2-iminoxypropionic acid

82



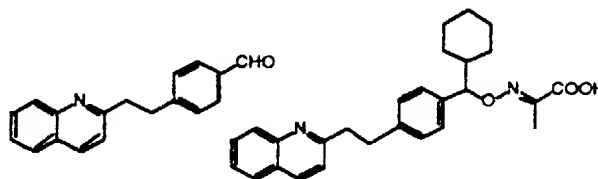
[Cyclohexyl-(1-methyl-6-(2-quinolylmethoxy)indol-2-yl)methyl]-2-iminoxypropionic acid

83



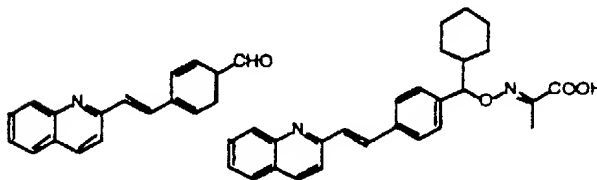
[Cycloheptyl-(6-(2-quinolylmethoxy)benzo[b]thien-2-yl)methyl]-2-iminoxypropionic acid

84



[Cyclohexyl-(4-(2-quinolylethyl)phenyl)methyl]-2-iminoxypropionic acid

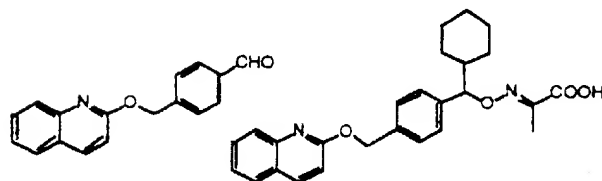
85



[Cyclohexyl-(4-(2-quinolylethenyl)phenyl)methyl]-2-iminoxypropionic acid

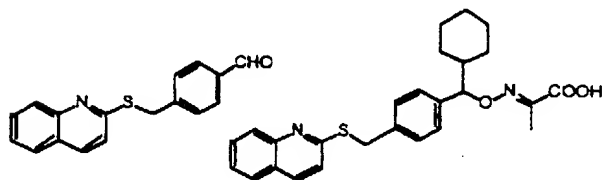
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86



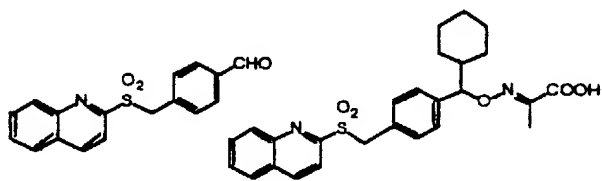
[Cyclohexyl-(4-(2-quinolyloxymethyl)phenyl)methyl]-2-iminoxypropionic acid

87



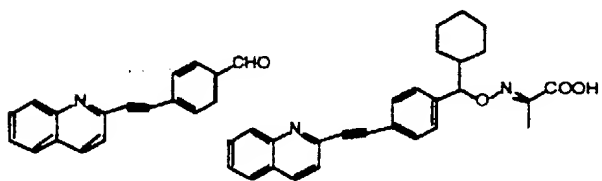
[Cyclohexyl-(4-(2-quinolythiomethyl)phenyl)methyl]-2-iminoxypropionic acid

88



[Cyclohexyl-(4-(2-quinolylsulfonylmethyl)phenyl)methyl]-2-iminoxypropionic acid

89

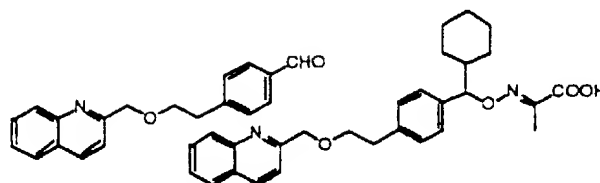


[Cyclohexyl-(4-(2-quinolyethynyl)phenyl)methyl]-2-iminoxypropionic acid



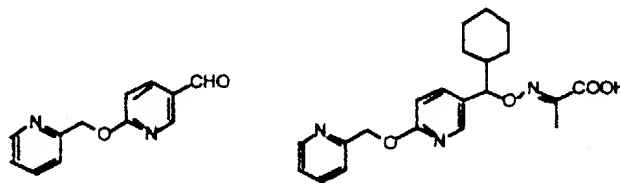
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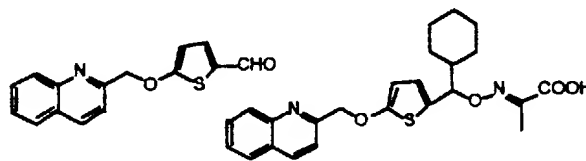
[Cyclohexyl-(4-(2-quinolylmethoxyethyl)phenyl)methyl]-2-iminoxypropionic acid

91



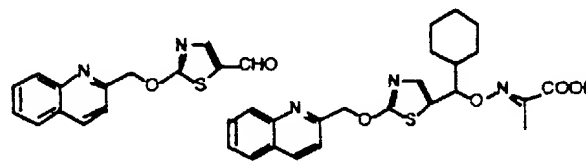
[Cyclohexyl-(2-(2-pyridylmethoxy)pyrid-5-yl)methyl]-2-iminoxypropionic acid

92



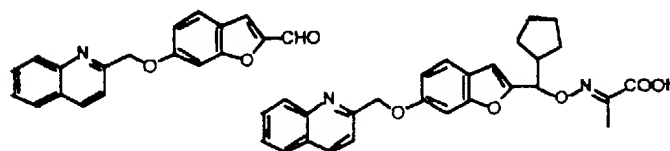
[Cyclohexyl-(5-(2-quinolylmethoxy)thien-2-yl)methyl]-2-iminoxypropionic acid

93



[Cyclohexyl-(2-(2-quinolylmethoxy)thien-5-yl)methyl]-2-iminoxypropionic acid

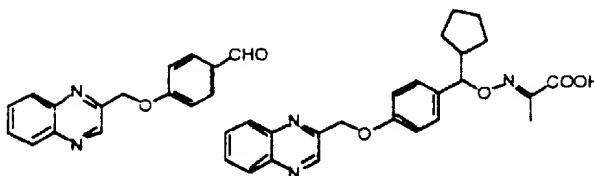
94



[Cyclohexyl-(6-(2-quinolylmethoxy)benzo[b]fur-2-yl)methyl]-2-iminoxypropionic acid

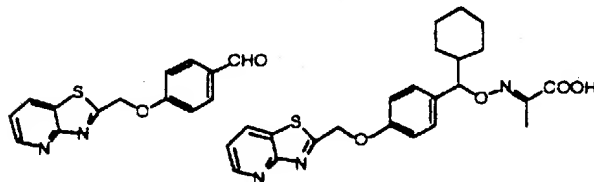
76

95



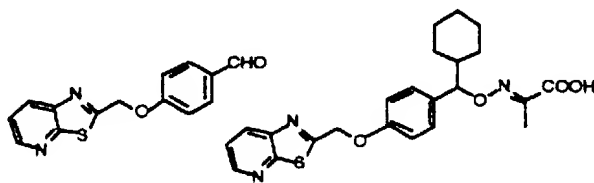
[Cyclopentyl-(4-(2-quinoxalylmethoxy)phenyl)methyl]-2-iminoxypropionic acid

96



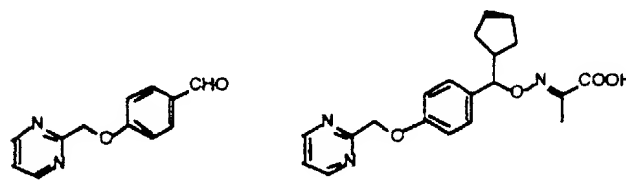
[Cyclohexyl-(4-(thiazolo[4,5-b]pyrid-6-ylmethoxy)phenyl)methyl]-2-iminoxypropionic acid

97



[Cyclohexyl-(4-(thiazolo[5,4-b]pyrid-6-ylmethoxy)phenyl)methyl]-2-iminoxypropionic acid

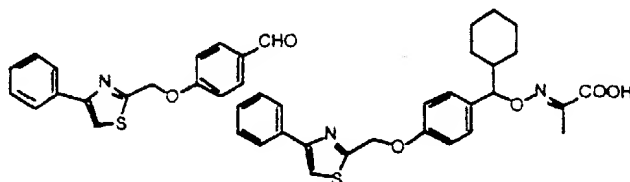
98



[Cyclopentyl-(4-(2-pyrimidylmethoxy)phenyl)methyl]-2-iminoxypropionic acid

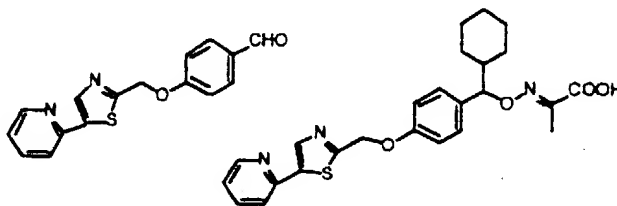
77

99



[Cyclohexyl-(4-(4-phenylthiazol-2-ylmethoxy)phenyl)methyl]-2-iminoxypropionic acid

100



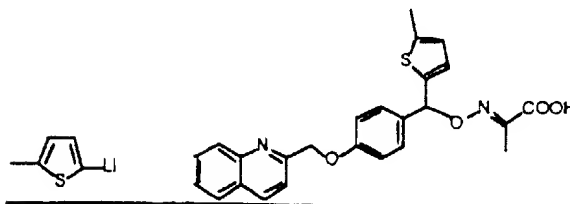
[Cyclohexyl-(4-((4-pyrid-2-yl)thiazol-2-ylmethoxy)phenyl)methyl]-2-iminoxypropionic acid

The following examples of this invention shown in Table 5 are prepared according to the method of Example 2 substituting the requisite organometallic addition reagent shown in Table 5 for cyclohexylmagnesium bromide.

Table 5.

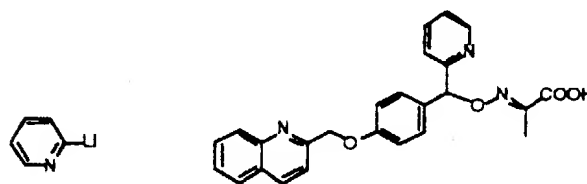
Example	Organometallic Reagent	Product
101		<p>[Phenyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypropionic acid</p>

102



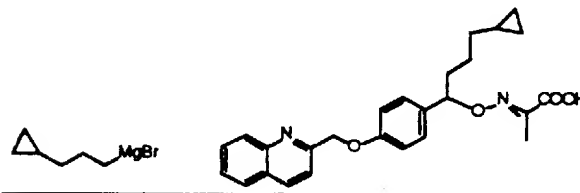
[5-Methylthien-2-yl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypionic acid

103



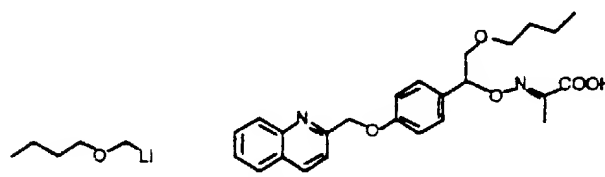
[Pyrid-2-yl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypionic acid

104



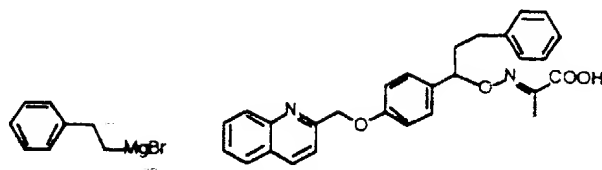
[3-Cyclopropylpropyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypionic acid

105



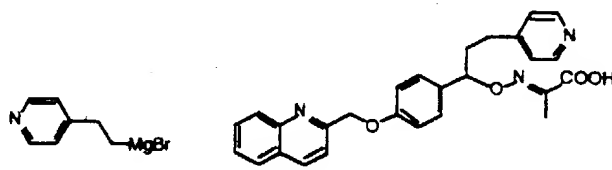
[Butyloxymethyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypionic acid

106



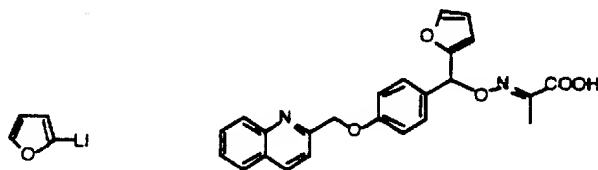
[2-Phenylethyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypropionic acid

107



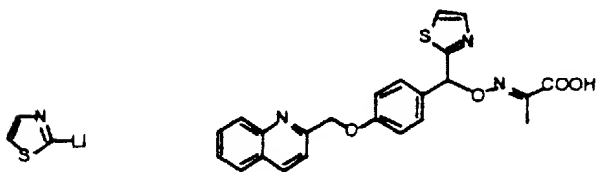
[2-Pyrid-4-ylethyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypropionic acid

108



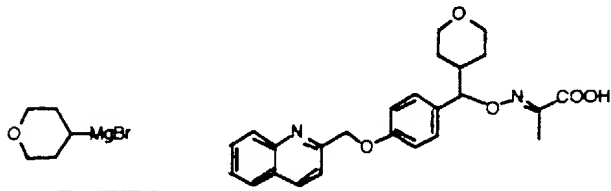
[2-Furyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypropionic acid

109



[2-Thiazolyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypropionic acid

110



[4-Perhydropyranyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypropionic acid

The compounds shown in Table 6 are prepared by converting the carboxylate examples described above into the corresponding hydroxyamides named as follows using known procedures in the literature to effect this functional transformation: for example by reacting the carboxylate example with oxalyl chloride to provide the corresponding acyl chloride intermediate which is directly treated with the requisite hydroxyl amine to provide the named examples that follow in Table 6.

10

Table 6

Example	Hydroxyamide
111	[Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]iminoxyaceto- <i>N</i> -hydroxyamide
112	[Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxy propionyl- <i>N</i> -methyl- <i>N</i> -hydroxyamide
113	[Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-4-iminoxy pentanoyl- <i>N</i> -methyl- <i>N</i> -hydroxyamide
114	[Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxy-3- (4-hydroxyphenyl)propionyl- <i>N</i> -methyl- <i>N</i> -hydroxyamide
115	[Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxy-3- phenylpropionyl- <i>N</i> -methyl- <i>N</i> -hydroxyamide
116	[Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-3-iminoxy- (2,2-dimethyl) propionyl- <i>N</i> -methyl- <i>N</i> -hydroxyamide
117	[Cyclopentyl-(4-(2-quinolylmethoxy)phenyl)methyl]iminoxy aceto- <i>N</i> -hydroxyamide
118	[Cyclopentyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxy propionyl- <i>N</i> -methyl- <i>N</i> -hydroxyamide

- 119 [1,2,3,4-Tetrahydro-6-(2-quinolylmethoxy)naphth-1-yl]iminoxy  
aceto-*N*-hydroxyamide
- 120 [1,2,3,4-Tetrahydro-6-(2-quinolylmethoxy)naphth-1-yl]-2-  
iminoxypropionyl-*N*-methyl-*N*-hydroxyamide
- 121 [4-(4-Chlorophenyl)-1-(4-(2-quinolylmethoxy)phenyl)  
butyl]iminoxyaceto-*N*-hydroxyamide
- 122 [2-Cyclohexyl-1-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]  
iminoxyaceto-*N*-hydroxyamide
- 123 [2-Cyclohexyl-1-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]-2-  
iminoxypropionyl-*N*-methyl-*N*-hydroxyamide
- 124 [2-Cyclohexyl-1-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]-4-  
iminoxypentanoyl-*N*-methyl-*N*-hydroxyamide
- 125 [Cycloheptyl-(4-(2-quinolylmethoxy)phenyl)methyl]iminoxy aceto-  
*N*-hydroxyamide
- 126 [3-Cyclohexyl-2-(4-(2-quinolylmethoxy)phenyl)prop-1-yl]iminoxy  
aceto-*N*-hydroxyamide
- 127 [3-Cyclohexyl-2-(4-(2-quinolylmethoxy)phenyl)prop-1-yl]-2-  
iminoxypropionyl-*N*-methyl-*N*-hydroxyamide
- 128 [3-Cyclohexyl-2-(4-(2-quinolylmethoxy)phenyl)prop-1-yl]-3-  
iminoxy-(2,2-dimethyl)propionyl-*N*-methyl-*N*-hydroxyamide
- 129 [4-(4-Fluorophenyl)-1-(4-(2-quinolylmethoxy)phenyl)but-1-yl]  
iminoxyaceto-*N*-hydroxyamide
- 130 [4-(4-Fluorophenyl)-1-(4-(2-quinolylmethoxy)phenyl)but-1-yl]-2-  
iminoxypropionyl-*N*-methyl-*N*-hydroxyamide

- 131 [2-Cyclohexyl-2-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]-  
iminoxyaceto-*N*-hydroxyamide
- 132 [2-Cycloheptyl-2-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]  
iminoxyaceto-*N*-hydroxyamide
- 133 [2-Cycloheptyl-2-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]-3-  
iminoxy-2,2-dimethylpropionyl-*N*-methyl-*N*-hydroxyamide
- 134 [2-Cyclopentyl-2-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]  
iminoxyaceto-*N*-hydroxyamide
- 135 [Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*Z*-2-iminoxy  
propionyl-*N*-methyl-*N*-hydroxyamide
- 136 [Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*E*-2-iminoxy  
propionyl-*N*-methyl-*N*-hydroxyamide
- 137 (R)-[Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*E*-2-  
iminoxypropionyl-*N*-methyl-*N*-hydroxyamide
- 138 (S)-[Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*E*-2-  
iminoxypropionyl-*N*-methyl-*N*-hydroxyamide
- 139 [Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*E*-iminoxy  
aceto-*N*-hydroxyamide
- 140 [2-phenyl-1-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]-*Z*-2-iminoxy  
propionyl-*N*-methyl-*N*-hydroxyamide
- 141 [2-phenyl-1-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]-*E*-2-iminoxy  
propionyl-*N*-methyl-*N*-hydroxyamide
- 142 [2-thienyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*E*-2-iminoxy  
propionyl-*N*-methyl-*N*-hydroxyamide



- 143 [Cyclohexyl-(2-chloro-4-(2-quinolylmethoxy)phenyl)methyl]-*E*-2-iminoxypropionyl-*N*-methyl-*N*-hydroxyamide
- 144 [Cyclohexyl-(3-chloro-4-(2-quinolylmethoxy)phenyl)methyl]-*E*-2-iminoxypropionyl-*N*-methyl-*N*-hydroxyamide
- 145 [Cyclohexyl-(2-chloro-4-(2-quinolylmethoxy)phenyl)methyl]-*Z*-2-iminoxypropionyl-*N*-methyl-*N*-hydroxyamide
- 146 [3-Methyl-3-phenyl-1-[4-(2-quinolylmethoxy)phenyl]but-1-yl]-*Z*-2-iminoxypropionyl-*N*-methyl-*N*-hydroxyamide
- 147 [3-Methyl-3-phenyl-1-(4-(2-quinolylmethoxy)phenyl)but-1-yl]-*E*-2-iminoxypropionyl-*N*-methyl-*N*-hydroxyamide
- 148 [3-Methyl-3-phenyl-1-(4-(2-quinolylmethoxy)phenyl)but-1-yl]-*E*-2-iminoxyacetic
- 149 [4-(2-Quinolylmethoxy)phenyl]pent-1-yl]-*E*-2-iminoxypropionyl-*N*-methyl-*N*-hydroxyamide
- 150 [4-(2-Quinolylmethoxy)phenyl]pent-1-yl]-*E*-iminoxyaceto-*N*-hydroxyamide
- 151 [4-(2-Quinolylmethoxy)phenyl]-but-3-en-1-yl]-*E*-iminoxy-2-propionyl-*N*-methyl-*N*-hydroxyamide
- 152 [Cyclohexyl-1-(4-(2-quinolylmethoxy)phenyl)eth-2-yl]-2-iminoxypropionyl-*N*-methyl-*N*-hydroxyamide
- 153 [Cycloheptyl-(4-(2-quinolylmethoxy)phenyl)eth-2-yl]-2-iminoxypropionyl-*N*-methyl-*N*-hydroxyamide
- 154 [2-chloro-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypropionyl-*N*-methyl-*N*-hydroxyamide

- 155 [Cycloheptyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxy  
propionyl-*N*-methyl-*N*-hydroxyamide
- 156 (R)-[Cyclopentyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*E*-2-  
iminoxypropionyl-*N*-methyl-*N*-hydroxyamide
- 157 (S)-[Cyclopentyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*E*-2-  
iminoxypropionyl-*N*-methyl-*N*-hydroxyamide
- 158 [Cyclohexyl-(4-(2-quinolylmethoxy)benzo[b]thien-2-yl)methyl]-2-  
iminoxypropionyl-*N*-methyl-*N*-hydroxyamide
- 159 [Cyclohexyl-(6-(2-quinolylmethoxy)pyrid-3-yl)methyl]iminoxy  
aceto-*N*-hydroxyamide
- 160 [Cyclohexyl-(4-(6-(4-fluorophenoxy)pyrid-2-ylmethoxy)phenyl)  
methyl]iminoxyaceto-*N*-hydroxyamide
- 161 [2-Cyclohexyl-1-(4-(4-thiazolylmethoxy)phenyl)eth-1-yl]iminoxy  
aceto-*N*-hydroxyamide
- 162 [2-Cyclohexyl-1-(4-(4-thiazolylmethoxy)phenyl)eth-1-yl]-2-  
iminoxypropionyl-*N*-methyl-*N*-hydroxyamide
- 163 [Cyclohexyl-(4-(4-thiazolylmethoxy)phenyl)methyl]-2-iminoxy  
propionyl-*N*-methyl-*N*-hydroxyamide
- 164 [Cyclohexyl-(4-(4-thiazolylmethoxy)phenyl)methyl]iminoxyaceto-  
*N*-hydroxyamide
- 165 [Cyclohexyl-(4-(2-benzothiazolylmethoxy)phenyl)methyl]iminoxy  
aceto-*N*-hydroxyamide
- 167 [Cyclohexyl-(4-(1-methyl-2-benzimidazolylmethoxy)phenyl)  
methyl]-2-iminoxypropionyl-*N*-methyl-*N*-hydroxyamide

168 [Cyclohexyl-(4-(2-benzoxazolylmethoxy)phenyl)methyl]  
iminoxyaceto-*N*-hydroxyamide

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5 The foregoing examples are merely illustrative of the invention and are not intended to limit the invention to the disclosed compounds. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which is defined in the appended claims.

## WHAT IS CLAIMED IS:

1. A compound of formula



5 or a pharmaceutically acceptable salt thereof wherein

n is zero or 1 with the proviso that n is zero when Y is tetrahydronaphthyl;

W is selected from the group consisting of

- 10 (a) phenyl,  
(b) phenyl substituted with  
halogen,  
nitrile,  
alkyl of one to six carbon atoms,  
15 alkoxy of one to six carbon atoms,  
thiazolyl,  
thiazolyl substituted with  
halogen,  
alkyl of one to six carbon atoms, or  
20 alkoxy of one to six carbon atoms,  
pyridyl, or  
pyridyl substituted with  
halogen,  
alkyl of one to six carbon atoms, or  
25 alkoxy of one to six carbon atoms,  
(c) naphthyl,  
(d) naphthyl substituted with  
halogen,  
alkyl of one to six carbon atoms, or  
30 alkoxy of one to six carbon atoms,  
(e) pyridyl,

- (f) pyridyl substituted with  
halogen,  
alkyl of one to six carbon atoms,  
alkoxy of one to six carbon atoms,  
phenoxy, or  
phenoxy substituted with  
halogen,  
alkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,
- (g) quinolyl,
- (h) quinolyl substituted with  
halogen,  
alkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,
- (i) benzothienyl,
- (j) benzothienyl substituted with  
halogen,  
alkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,
- (k) benzothiazolyl,
- (l) benzothiazolyl substituted with  
halogen,  
alkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,
- (m) benzoxazolyl,
- (n) benzoxazolyl substituted with  
halogen,  
alkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,
- (o) benzimidazolyl,
- (p) benzimidazolyl substituted with  
halogen,  
alkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,
- (r) quinoxalinylyl,

- 70 (s) quinoxalinyI substituted with  
halogen,  
alkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,
- (t) pyrimidyl,  
75 (u) pyrimidyl substituted with  
halogen,  
alkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,
- (v) thiazolyl,  
80 (w) thiazolyl substituted with  
halogen,  
alkyl of one to six carbon atoms,  
alkoxy of one to six carbon atoms,  
phenyl,  
phenyl substituted with  
halogen,  
85 alkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,  
pyridyl, or  
pyridyl substituted with  
halogen,  
90 alkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,
- (x) pyridothiazolyl, and  
(y) pyridothiazolyl substituted with  
halogen,  
95 alkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms;

X is selected from the group consisting of  
alkylene of one to six carbon atoms,  
100 alkenylene of two to six carbon atoms,  
alkynylene of two to six carbon atoms,  
alkoxy of one to six carbon atoms,  
thioalkyloxy of one to six carbon atoms, and  
alkylsulfonyl of one to six carbon atoms,

105

Q is a valence bond or is selected from the group consisting of  
-O-,  
-S-,  
>NR<sup>4</sup> where R<sup>4</sup> is hydrogen, or alkyl of one to six carbon atoms,  
110 and  
>NCOR<sup>5</sup> where R<sup>5</sup> is alkyl of one to six carbon atoms, amino, or  
alkylamino of one to six carbon atoms;

Y is selected from the group consisting of  
115 (a) phenyl,  
(b) phenyl substituted with  
halogen,  
alkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,  
120 (c) biphenyl,  
(d) biphenyl substituted with  
halogen,  
alkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,  
125 (e) naphthyl,  
(f) naphthyl substituted with  
halogen,  
alkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,  
130 (g) tetrahydronaphthyl,

- 135 (h) tetrahydronaphthyl substituted with  
halogen,  
alkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,
- (i) indolyl,
- 140 (j) indolyl substituted with  
halogen,  
alkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,
- (k) benzothienyl,
- 145 (l) benzothienyl substituted with  
halogen,  
alkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,
- (m) pyridyl,
- 150 (n) pyridyl substituted with  
halogen,  
alkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,
- (o) thienyl,
- 155 (p) thienyl substituted with  
halogen,  
alkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,
- (q) thiazolyl,
- 180 (r) thiazolyl substituted with  
halogen,  
alkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,
- (s) benzo[b]furyl,
- 185 (t) benzo[b]furyl substituted with  
halogen,  
alkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,
- (u) benzo[b]thiazolyl,



- 170 (v) benzo[b]thienyl substituted with  
halogen,  
alkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms, and
- (w) thiazolylphenyl, and
- 175 (x) thiazolylphenyl substituted with  
halogen,  
alkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms;
- 180  $R^1$  is selected from the group consisting of
- (a) alkyl of one to twelve carbon atoms,  
(b) cycloalkyl of three to ten carbon atoms,  
(c) cycloalkyl of three to ten carbon atoms containing one atom selected  
from
- 185 -O-,  
-S-,  
>NR<sup>4</sup> where R<sup>4</sup> is hydrogen, or alkyl of one to six carbon  
atoms, and  
>NCOR<sup>5</sup> where R<sup>5</sup> is alkyl of one to six carbon atoms,  
amino, or aminoalkyl of one to six carbon atoms,
- 190 (d) alkoxyalkyl in which the alkoxy and alkyl portions independently are  
of one to twelve carbon atoms,  
(e) phenyl,  
(f) phenyl substituted with
- 195 halogen,  
alkyl of one to six carbon atoms,  
haloalkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,  
(g) phenylalkyl in which the alkyl portion is of one to six carbon atoms,

- 200 (h) phenylalkyl in which the alkyl portion is of one to six carbon atoms,  
and the phenyl ring is substituted with  
halogen,  
alkyl of one to six carbon atoms,  
haloalkyl of one to six carbon atoms, or  
205 alkoxy of one to six carbon atoms,
- (i) pyridyl,  
(j) pyridyl substituted with  
halogen,  
alkyl of one to six carbon atoms,  
210 haloalkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,
- (k) thiazolyl,  
(l) thiazolyl substituted with  
halogen,  
215 alkyl of one to six carbon atoms,  
haloalkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,
- (m) thienyl,  
(n) thienyl substituted with  
halogen,  
220 alkyl of one to six carbon atoms,  
haloalkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,
- (o) furyl,  
225 (p) furyl substituted with  
halogen,  
alkyl of one to six carbon atoms,  
haloalkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,
- 230 (q) oxazolyl,  
(r) oxazolyl substituted with  
halogen,  
alkyl of one to six carbon atoms,  
haloalkyl of one to six carbon atoms, or  
235 alkoxy of one to six carbon atoms,

- 240 (s) pyridazolyl,  
(t) pyridazolyl substituted with  
halogen,  
alkyl of one to six carbon atoms,  
haloalkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,
- 245 (u) pyridylalkyl wherein the alkyl portion is of one to six carbon atoms,  
(v) pyridylalkyl wherein the alkyl portion is of one to six carbon atoms,  
and the pyridyl ring is substituted with  
halogen,  
alkyl of one to six carbon atoms,  
haloalkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,
- 250 (w) thiazolylalkyl wherein the alkyl portion is of one to six carbon atoms,  
(x) thiazolylalkyl wherein the alkyl portion is of one to six carbon atoms,  
and the thiazolyl ring is substituted with  
halogen,  
alkyl of one to six carbon atoms,  
haloalkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,
- 255 (y) thienylalkyl wherein the alkyl portion is of one to six carbon atoms,  
(z) thienylalkyl wherein the alkyl portion is of one to six carbon atoms,  
and the thienyl ring is substituted with  
halogen,  
alkyl of one to six carbon atoms,  
haloalkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,
- 260 (aa) furylalkyl wherein the alkyl portion is of one to six carbon atoms,  
(bb) furylalkyl wherein the alkyl portion is of one to six carbon atoms,  
and the furyl ring is substituted with  
halogen,  
alkyl of one to six carbon atoms,  
haloalkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,
- 265 (cc) oxazolylalkyl wherein the alkyl portion is of one to six carbon atoms,
- 270

- 275 (dd) oxazolylalkyl wherein the alkyl portion is of one to six carbon atoms,  
and the oxazolyl ring is substituted with  
halogen,  
alkyl of one to six carbon atoms,  
haloalkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,
- (ee) pyridazolylalkyl wherein the alkyl portion is of one to six carbon  
atoms, and
- 280 (ff) pyridazolylalkyl wherein the alkyl portion is of one to six carbon  
atoms, and the pyridazolyl ring is substituted with  
halogen,  
alkyl of one to six carbon atoms,  
haloalkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms;

285

$R^2$  is selected from the group consisting of  
hydrogen,  
alkyl of one to six carbon atoms, and  
hydroxyalkyl of one to six carbon atoms;

290

A is a valence bond or is selected from the group consisting of:

- (a) alkylene of one to six carbon atoms,  
(b) cycloalkylene of three to eight carbon atoms,  
(c) phenyl,  
295 (d) phenyl substituted with  
halogen,  
alkyl of one to six carbon atoms,  
haloalkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,
- 300 (e) phenylalkyl in which the alkyl portion is of one to six carbon atoms,

- (f) phenylalkyl in which the alkyl portion is of one to six carbon atoms,  
and the phenyl ring is substituted with  
halogen,  
alkyl of one to six carbon atoms,  
haloalkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms;
- (g) pyridyl,
- (h) pyridyl substituted with  
halogen,  
alkyl of one to six carbon atoms,  
haloalkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,
- (i) thiazolyl,
- (j) thiazolyl substituted with  
halogen,  
alkyl of one to six carbon atoms,  
haloalkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,
- (k) thienyl,
- (l) thienyl substituted with  
halogen,  
alkyl of one to six carbon atoms,  
haloalkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,
- (m) furyl,
- (n) furyl substituted with  
halogen,  
alkyl of one to six carbon atoms,  
haloalkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,
- (o) oxazolyl,
- (p) oxazolyl substituted with  
halogen,  
alkyl of one to six carbon atoms,  
haloalkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,

- 340 (q) pyridylalkyl wherein the alkyl portion is of one to six carbon atoms,  
(r) pyridylalkyl wherein the alkyl portion is of one to six carbon atoms,  
and the pyridyl ring is substituted with  
halogen,  
alkyl of one to six carbon atoms,  
haloalkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,
- 345 (s) thiazolylalkyl wherein the alkyl portion is of one to six carbon atoms,  
(t) thiazolylalkyl wherein the alkyl portion is of one to six carbon atoms,  
and the thiazolyl ring is substituted with  
halogen,  
alkyl of one to six carbon atoms,  
haloalkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,
- 350 (u) thienylalkyl wherein the alkyl portion is of one to six carbon atoms,  
(v) thienylalkyl wherein the alkyl portion is of one to six carbon atoms,  
and the thienyl ring is substituted with  
halogen,  
alkyl of one to six carbon atoms,  
haloalkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,
- 355 (w) furylalkyl wherein the alkyl portion is of one to six carbon atoms,  
(x) furylalkyl wherein the alkyl portion is of one to six carbon atoms,  
and the furyl ring is substituted with  
halogen,  
alkyl of one to six carbon atoms,  
haloalkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,
- 365 (y) oxazolylalkyl wherein the alkyl portion is of one to six carbon atoms,  
(z) oxazolylalkyl wherein the alkyl portion is of one to six carbon atoms,  
and the oxazolyl ring is substituted with  
halogen,  
alkyl of one to six carbon atoms,  
haloalkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms; and
- 370

M is selected from the group consisting of

a pharmaceutically acceptable, metabolically cleavable group,

375 -OR<sup>6</sup> where R<sup>6</sup> is selected from hydrogen or alkyl of one to six carbon atoms,

-NR<sup>6</sup>R<sup>7</sup> wherein R<sup>7</sup> is selected from

hydrogen,

380 alkyl of one to six carbon atoms,

hydroxy,

alkoxy or one to six carbon atoms, or

R<sup>6</sup> and R<sup>7</sup> taken together define a five- to eight-membered ring optionally containing one or two additional oxygen, sulfur and nitrogen atoms,

385 -NH-tetrazolyl,

-NH-2-, 3-, or 4-pyridyl, and

-NH-2-, 4-, or 5-thiazolyl.

2. A compound as defined in Claim 1, or a pharmaceutically acceptable salt thereof wherein W is selected from the group consisting of

phenyl,

phenyl substituted with

5 halogen,

nitrile,

alkyl of one to six carbon atoms,

alkoxy of one to six carbon atoms,

thiazolyl,

10 thiazolyl substituted with

halogen,

alkyl of one to six carbon atoms, or

alkoxy of one to six carbon atoms, or

pyridyl,

15 pyridyl substituted with

halogen,

alkyl of one to six carbon atoms, or

alkoxy of one to six carbon atoms,

naphthyl, and

naphthyl substituted with  
halogen,  
alkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms.

25

3. A compound as defined in Claim 2 or a pharmaceutically acceptable salt thereof wherein Q is -O-.
4. A compound as defined in Claim 3, or a pharmaceutically acceptable salt thereof wherein Y is phenyl, or phenyl substituted with halogen, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms, and X is alkylene of one to six carbon atoms.

5

5. A compound as defined in Claim 1 or a pharmaceutically acceptable salt thereof wherein W is selected from the group consisting of

pyridyl,  
pyridyl substituted with

5

halogen,  
alkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,  
phenoxy, and  
phenoxy substituted with

10

halogen,  
alkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,

quinolyl,  
quinolyl substituted with

15

halogen,  
alkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,

benzothienyl,  
benzothienyl substituted with

20

halogen,  
alkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms,  
benzothiazolyl,



- 25                    benzothiazolyl substituted with  
                     halogen,  
                     alkyl of one to six carbon atoms, or  
                     alkoxy of one to six carbon atoms,  
                     benzoxazolyl,  
                     benzoxazolyl substituted with  
30                    halogen,  
                     alkyl of one to six carbon atoms, or  
                     alkoxy of one to six carbon atoms,  
                     benzimidazolyl,  
                     benzimidazolyl substituted with  
35                    halogen,  
                     alkyl of one to six carbon atoms, or  
                     alkoxy of one to six carbon atoms,  
                     quinoxalinylyl,  
                     quinoxalinylyl substituted with  
40                    halogen,  
                     alkyl of one to six carbon atoms, or  
                     alkoxy of one to six carbon atoms,  
                     pyrimidyl,  
                     pyrimidyl substituted with  
45                    halogen,  
                     alkyl of one to six carbon atoms, or  
                     alkoxy of one to six carbon atoms,  
                     thiazolyl,  
                     thiazolyl substituted with  
50                    phenyl,  
                     phenyl substituted with  
                     halogen,  
                     alkyl of one to six carbon atoms, or  
                     alkoxy of one to six carbon atoms,  
55                    pyridyl, or  
                     pyridyl substituted with  
                     halogen,  
                     alkyl of one to six carbon atoms, or  
                     alkoxy of one to six carbon atoms,

60 pyridothiazolyl, and  
pyridothiazolyl substituted with  
halogen,  
alkyl of one to six carbon atoms, or  
alkoxy of one to six carbon atoms;

65

6. A compound as defined in Claim 5, or a pharmaceutically acceptable salt thereof wherein Y is phenyl, or phenyl substituted with halogen, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms and W is quinolyl, or quinolyl substituted with halogen, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms.

5

7. A compound as defined in Claim 1, or a pharmaceutically acceptable salt thereof selected from the group consisting of  
[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]iminoxyacetic acid,  
[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxy propionic acid,  
5 [cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-4-iminoxy pentanoic acid,  
[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxy-3-(4-hydroxyphenyl)propionic acid,  
10 [cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxy-3-phenylpropionic acid,  
O-[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-4-carboxybenzaldoxime,  
[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-3-iminoxy-(2,2-dimethyl) propionic acid,  
15 [cyclopentyl-(4-(2-quinolylmethoxy)phenyl)methyl]iminoxy acetic acid,  
[cyclopentyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxy propionic acid,  
[1,2,3,4-tetrahydro-6-(2-quinolylmethoxy)naphth-1-yl]iminoxy acetic acid,  
20 [1,2,3,4-tetrahydro-6-(2-quinolylmethoxy)naphth-1-yl]-2-iminoxypropionic acid,  
[4-(4-chlorophenyl)-1-(4-(2-quinolylmethoxy)phenyl)butyl]iminoxyacetic acid,  
[2-cyclohexyl-1-(4-(2-quinolylmethoxy)phenyl)eth-1-yl] iminoxyacetic acid,

- 25      *O*-[2-cyclohexyl-1-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]-4-carboxybenzaldoxime,  
[2-cyclohexyl-1-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]-2-iminoxypropionic acid,  
[2-cyclohexyl-1-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]-4-iminoxy-  
30      pentanoic acid,  
[cycloheptyl-(4-(2-quinolylmethoxy)phenyl)methyl]iminoxy acetic acid,  
[3-cyclohexyl-2-[4-(2-quinolylmethoxy)phenyl]prop-1-yl]iminoxy acetic acid,  
[3-cyclohexyl-2-(4-(2-quinolylmethoxy)phenyl)prop-1-yl]-2-  
35      iminoxypropionic acid,  
[3-cyclohexyl-2-(4-(2-quinolylmethoxy)phenyl)prop-1-yl]-3-iminoxy-(2,2-dimethyl)propionic acid,  
[4-(4-fluorophenyl)-1-(4-(2-quinolylmethoxy)phenyl)but-1-yl] iminoxyacetic acid,  
40      [4-(4-fluorophenyl)-1-(4-(2-quinolylmethoxy)phenyl)but-1-yl]-2-iminoxypropionic acid,  
[2-cyclohexyl-2-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]-iminoxyacetic acid,  
[2-cycloheptyl-2-(4-(2-quinolylmethoxy)phenyl)eth-1-yl] iminoxyacetic  
45      acid,  
[2-cycloheptyl-2-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]-3-iminoxy-2,2-dimethylpropionic acid,  
[2-cyclopentyl-2-(4-(2-quinolylmethoxy)phenyl)eth-1-yl] iminoxyacetic acid,  
50      [cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*Z*-2-iminoxypropionic acid methyl ester,  
[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*E*-2-iminoxypropionic acid methyl ester,  
[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*Z*-2-iminoxy propionic  
55      acid,  
[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*E*-2-iminoxy propionic acid,  
(*R*)-[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*E*-2-iminoxypropionic acid methyl ester,

- 60 (R)-[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*E*-2-  
iminoxypropionic acid,  
(S)-[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*E*-2-  
iminoxypropionic acid methyl ester,  
(S)-[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*E*-2-  
65 iminoxypropionic acid,  
[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*Z*-iminoxy acetic acid  
methyl ester,  
[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*E*-iminoxy acetic acid  
methyl ester,  
70 [cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*E*-iminoxy acetic acid,  
[2-phenyl-1-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]-*Z*-2-iminoxy propionic  
acid,  
[2-phenyl-1-(4-(2-quinolylmethoxy)phenyl)eth-1-yl]-*E*-2-iminoxy propionic  
acid,  
75 [2-thienyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*E*-2-iminoxy propionic  
acid,  
[cyclohexyl-(2-chloro-4-(2-quinolylmethoxy)phenyl)methyl]-*E*-2-  
iminoxypropionic acid,  
[cyclohexyl-(3-chloro-4-(2-quinolylmethoxy)phenyl)methyl]-*E*-2-  
80 iminoxypropionic acid,  
[cyclohexyl-(2-chloro-4-(2-quinolylmethoxy)phenyl)methyl]-*Z*-2-  
iminoxypropionic acid,  
[3-methyl-3-phenyl-1-(4-(2-quinolylmethoxy)phenyl)but-1-yl]-*Z*-2-  
iminoxypropionic acid,  
85 [3-methyl-3-phenyl-1-(4-(2-quinolylmethoxy)phenyl)but-1-yl]-*E*-2-  
iminoxypropionic acid,  
[3-methyl-3-phenyl-1-(4-(2-quinolylmethoxy)phenyl)but-1-yl]-*E*-2-  
iminoxyacetic,  
[4-(2-quinolylmethoxy)phenyl]pent-1-yl]-*E*-2-iminoxypropionic acid,  
90 [4-(2-quinolylmethoxy)phenyl]pent-1-yl]-*E*-iminoxyacetic acid,  
[4-(2-quinolylmethoxy)phenyl]-but-3-en-1-yl]-*E*-iminoxy-2-propionic acid,  
[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*E*-2-iminoxy butanoic  
acid,  
[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-*E*-3-iminoxybutanoic  
95 acid,

- [cyclohexyl-1-(4-(2-quinolylmethoxy)phenyl)eth-2-yl]-2-iminoxy propionic acid,
- [cycloheptyl-(4-(2-quinolylmethoxy)phenyl)eth-2-yl]-2-iminoxy propionic acid,
- 100 [2-chloro-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxy propionic acid,  
[cycloheptyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxy propionic acid,
- sodium [cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypropionate,
- 105 (R)-[cyclopentyl-(4-(2-quinolylmethoxy)phenyl)methyl]-E-2-iminoxypropionic acid,  
(S)-[cyclopentyl-(4-(2-quinolylmethoxy)phenyl)methyl]-E-2-iminoxypropionic acid,
- [cyclohexyl-(4-(2-quinolylmethoxy)benzo[b]thien-2-yl)methyl]-2-iminoxypropionic acid,
- 110 [cyclohexyl-(6-(2-quinolylmethoxy)pyrid-3-yl)methyl]iminoxy acetic acid,  
[cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxy propionic acid 2-thiazolylamide,
- [cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxy propionic acid 2-pyridylamide,
- 115 [cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypropionic acid 5-tetrazylamide,
- [Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]iminoxyacetic acid,  
[Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypropionic acid,
- 120 (R)-[Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypropionic acid,  
(S)-[Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypropionic acid,
- 125 [Cyclopentyl-(4-(2-quinolylmethoxy)phenyl)methyl]iminoxyacetic acid,  
[Cyclopentyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypropionic acid,
- (R)-[Cyclopentyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypropionic acid,
- 130 (S)-[Cyclopentyl-(4-(2-quinolylmethoxy)phenyl)methyl]-2-iminoxypropionic acid,

- [2-Cyclohexyl-1-(4-(2-quinolylmethoxy)phenyl)ethyl]iminoxyacetic acid,  
[cyclohexyl-(4-(2-benzothiazolylmethoxy)phenyl)methyl]iminoxy acetic  
acid,  
135 (R)-[cyclohexyl-(4-(2-benzothiazolylmethoxy)phenyl)methyl]iminoxy acetic  
acid,  
(S)-[cyclohexyl-(4-(2-benzothiazolylmethoxy)phenyl)methyl]iminoxy acetic  
acid,  
[cyclopentyl-(4-(2-benzothiazolylmethoxy)phenyl)methyl]iminoxy acetic  
140 acid.  
(R)-[cyclopentyl-(4-(2-benzothiazolylmethoxy)phenyl)methyl]iminoxy acetic  
acid,  
(S)-[cyclopentyl-(4-(2-benzothiazolylmethoxy)phenyl)methyl]iminoxy acetic  
acid,  
145 [2-cyclohexyl-1-(4-(4-thiazolylmethoxy)phenyl)eth-1-yl]iminoxy acetic acid,  
O-[2-cyclohexyl-1-(4-(4-thiazolylmethoxy)phenyl)eth-1-yl]-4-  
carboxybenzal doxime,  
[2-cyclohexyl-1-(4-(4-thiazolylmethoxy)phenyl)eth-1-yl]-2-iminoxy-  
propionic acid,  
150 [cyclohexyl-(4-(4-thiazolylmethoxy)phenyl)methyl]-2-iminoxy propionic  
acid,  
[cyclohexyl-(4-(4-thiazolylmethoxy)phenyl)methyl]iminoxyacetic acid,  
[2-cyclopentyl-1-(4-(4-thiazolylmethoxy)phenyl)eth-1-yl]iminoxy acetic  
acid,  
155 O-[2-cyclopentyl-1-(4-(4-thiazolylmethoxy)phenyl)eth-1-yl]-4-  
carboxybenzal doxime,  
[2-cyclopentyl-1-(4-(4-thiazolylmethoxy)phenyl)eth-1-yl]-2-iminoxy-  
propionic acid,  
[cyclopentyl-(4-(4-thiazolylmethoxy)phenyl)methyl]-2-iminoxy propionic  
160 acid, and  
[cyclopentyl-(4-(4-thiazolylmethoxy)phenyl)methyl]iminoxyacetic acid,  
[cyclohexyl-(4-(6-(4-fluorophenoxy)pyrid-2-ylmethoxy)phenyl)methyl]  
iminoxyacetic acid,  
(R)-[cyclohexyl-(4-(6-(4-fluorophenoxy)pyrid-2-ylmethoxy)phenyl)methyl]  
165 iminoxyacetic acid,  
(S)-[cyclohexyl-(4-(6-(4-fluorophenoxy)pyrid-2-ylmethoxy)phenyl)methyl]  
iminoxyacetic acid,

170 [cyclopentyl-(4-(6-(4-fluorophenoxy)pyrid-2-ylmethoxy)phenyl)methyl]  
iminoxyacetic acid,  
(R)-[cyclopentyl-(4-(6-(4-fluorophenoxy)pyrid-2-ylmethoxy)phenyl)methyl]  
iminoxyacetic acid, and  
(S)-[cyclopentyl-(4-(6-(4-fluorophenoxy)pyrid-2-ylmethoxy)phenyl)methyl]  
iminoxyacetic acid.

8. A composition for inhibiting lipoxygenase activity comprising a therapeutically effective amount of a compound in accordance with Claim 1 in combination with a pharmaceutically acceptable.
9. A method of inhibiting lipoxygenase activity in a mammal in need of such treatment comprising administering to the mammal a therapeutically effective amount of a compound in accordance with Claim 1.

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International Application No

PCT/US 95/08367

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US-A-5420282	30-05-95	NONE	
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US-A-5358955	25-10-94	CA-A- 2136076	11-05-94
		EP-A- 0666849	16-08-95
		WO-A- 9410148	11-05-94
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US-A-5399699	21-03-95	NONE	
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# INTERNATIONAL SEARCH REPORT

1. International application No.

PCT/US 95/08367

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Claim 9 relates to a method of treatment of the human/animal body by therapy (Art. 17(2)(b), R. 39.1(iv)PCT). The search has been carried out and based on the alleged effects of the compounds/compositions.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Int. Application No

PCT/US 95/08367

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	US,A,5 420 282 (BROOKS DEE W ET AL) 30 May 1995 see the whole document ---	1-8
P,X	US,A,5 358 955 (BROOKS DEE W ET AL) 25 October 1994 see the whole document ---	1-8
P,X	US,A,5 399 699 (KOLASA TEODOZYI ET AL) 21 March 1995 see the whole document -----	1-8

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 95/08367

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6	C07D215/14	A61K31/47	C07D277/24	C07D277/64	C07D213/30
	C07D235/12	C07D263/56	C07D241/42	C07D239/26	C07D215/26
	C07D215/36	C07D409/12	C07D401/12	C07D413/12	C07D405/12

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO,A,94 10148 (ABBOTT LAB) 11 May 1994 pages 2-3, pages 23-24 examples 6-7 ---	1-6,8 7
Y	US,A,5 326 883 (BROOKS DEE W ET AL) 5 July 1994 see table 3 ---	1-8
Y	EP,A,0 349 062 (MERCK FROSST CANADA INC) 3 January 1990 cited in the application see page 3 - page 4 ---	1-8
Y	US,A,4 970 215 (MOHRS KLAUS ET AL) 13 November 1990 cited in the application see the whole document ---	1-8
-/--		

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&amp;" document member of the same patent family

Date of the actual completion of the international search

10 October 1995

Date of mailing of the international search report

12.12.95

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